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Applicants:	Masahiko KOIKE et al.
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SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam/Sir:

1. I, Masahiko Koike, the undersigned, a citizen of Japan residing at 2-2-29, Senrien, Toyonaka-shi, Osaka 560-0046, JAPAN, do hereby declare:

2. I graduated from Toyama Medical and Pharmaceutical University with a degree of Master of Science in March 1991, and I was a visiting scientist in the Department of Industrial and Physical Pharmacy at Purdue University from April 2005 to March 2006.

3. I have been employed by Takeda Pharmaceutical Company Limited, Osaka, Japan, the Assignee of the present application, and have been engaged in pharmaceutical research therein since April 1991. I have not received any additional compensation for preparing this Declaration other than my normal compensation as an employee at Takeda Pharmaceutical Company Limited.

4. I am able to read and understand the English language when it is written.

5. I am one of the co-inventors of the present patent application.

6. I have reviewed the June 16, 2010 Office Action and the references cited therein.

7. I hereby submit this Declaration to supplement the Declaration submitted on July 24, 2009 and the Declaration submitted March 12, 2010.

8. The experimental results described below were obtained by either myself or another under my supervision.

Unexpected success provided by present invention

9. At the outset, the July 24, 2009 Declaration was not based only on an opinion but was based the results of the experiments conducted according to the Paddle method, as described on pp. 2-3 of the present Declaration, which also references the present Specification.

10. As provided in the July 24, 2009 Declaration, discrepancies between *in vitro* and clinical studies of a combination drug, which contained pioglitazone (pioglitazone hydrochloride) and metformin (metformin hydrochloride) as active ingredients, were observed when a median size of pioglitazone tested was above the micronized range (i.e., 2-10 μm). Specifically, when a combination drug with pioglitazone of a median size of 13 μm was administered to a human and the blood concentration profiles of these active ingredients were examined during *in vivo* clinical studies, the pioglitazone in the combination drug was not found to be bioequivalent to that in a drug ("Actos®") with pioglitazone as the single active ingredient. By contrast, during clinical studies, metformin in the combination drug was found to be bioequivalent to that in a drug ("Glucophage®") with metformin as the single active ingredient. The results of the bioequivalence determination are provided in Table DD1, and a summary thereof is provided in Table DD2. Note Table DD2 is the same as Table D1 presented in the July 24, 2009 Declaration and is provided herein again to facilitate the comparison and contrast.

Table DD1. Results of clinical studies demonstrating that bioequivalence of pioglitazone was not established when the particle size of pioglitazone was not "micronized" (i.e., 2-10 μm).

Clinical results of monolayer FDC (US, n=68)

"Non-micronized Pioglitazone used"

Formulation	FDC Non-micronized Pioglitazone used 15mg+500mg	Coadministered Actos® 15mg	Coadministered Glucophage® 500mg
Pioglitazone			
C_{max} (ng/mL)	577.8	690.9	-
AUC_{0-t} (h*ng/mL)	4591.3	5733.4	-
90% CI for Ratio (%)			
C_{max}	76.8-91.0	Not Bioequivalent	-
AUC_{0-t}	75.8-84.6		-
Metformin			
C_{max} (ng/mL)	1470.0	-	1427.6
AUC_{0-t} (h*ng/mL)	7170.8	-	7070.2
90% CI for Ratio (%)			
C_{max}	97.0-109.3	Bioequivalent	-
AUC_{0-t}	94.5-108.9		-

Acceptance range of the 90% CIs for the ratios: 80-125 %

Table DD2. Bioequivalence results of the two ingredients – pioglitazone and metformin as observed during *in vitro* dissolution test and clinical results.

Fixed Dose Combination (FDC)	*In vitro* Dissolution	Clinical Results
pioglitazone	Equivalent to Actos®	Not bioequivalent to Actos®
metformin	Not equivalent to Glucophage®	Bioequivalent to Glucophage®

11. These discrepancies can be eliminated, thereby achieving bioequivalence for both pioglitazone and metformin when the median particle size of pioglitazone in the present combination drug was reduced to between 2 and 10 μm ("micronized"). The results of the bioequivalence as established by the micronization of pioglitazone are provided in Table DD3. Even more surprisingly, it was observed that micronization of the pioglitazone had no significant effect upon the uniformity of both of the active pharmaceutical ingredients, as shown in Table DD4.

Table DD3. Results of clinical studies demonstrating that bioequivalence of pioglitazone was established when the particle size of pioglitazone was "micronized" (i.e., 2-10 μm).

Clinical results of micronized monolayer FDC (US, n=66)

Present invention

Formulation	FDC Micronized Pioglitazone used 15 mg + 500 mg	Coadministered Actos® 15mg	Coadministered Glucophage® 500mg
Pioglitazone			
C_{max} (ng/mL)	540.9	569.5	-
AUC_{0-t} (h*ng/mL)	4715.6	4827.1	-
90% CI for Ratio (%)			
C_{max}	86.2-104.7	Bioequivalent	-
AUC_{0-t}	91.0-104.9		-
Metformin			
C_{max} (ng/mL)	1160.1	-	1171.5
AUC_{0-t} (h*ng/mL)	7257.8	-	7073.4
90% CI for Ratio (%)			
C_{max}	94.8-103.4	Bioequivalent	-
AUC_{0-t}	97.9-107.5		-

Acceptance range of the 90% CIs for the ratios: 80-125 %

Table DD4. Non-micronized pioglitazone showed a fairly low variation level of the Active Pharmaceutical Ingredients (APIs), which level was comparable to that of the micronized pioglitazone. Therefore, micronization of pioglitazone had no significant effect upon the uniformity of both of the APIs.

Content uniformity of the APIs

	FDC **"Non-Micronized Pioglitazone used"**	**FDC** **"Micronized Pioglitazone used"** ***Present invention***
Pioglitazone HCl		
Range (%)	96.4-100.9	98.1-101.8
RSD (%)	1.6	1.1
Metformin HCl		
Range (%)	97.6-99.7	99.5-102.2
RSD (%)	0.8	1.0

In the experiments presented in Table DD4, the median particle size of metformin HCl: 29 μm; the median particle size of micronized pioglitazone: 7 μm; the median particle size of non-micronized pioglitazone: 18.5 μm (as a mixture with microcrystalline cellulose) and 13 μm (as the sole compound).

12. Dissolution Test of Pioglitazone HCl 15mg / Metformin HCl 500mg or 800mg

Test condition: Paddle Method (50 rpm) using a McIlvaine buffer (900 mL, 37°C, pH 2.5)

Please note that the above test was conducted under the higher pH and lower dissolution of pioglitazone HCl than the test condition described in Specification (Paddle Method (50 rpm) using a hydrochloric acid-potassium chloride buffer (900 mL, 37°C, pH 2.0)). Under such condition, the dissolution rate is more susceptible to the effect of hardness of the tablet (which is a severe condition where the dissolution rate is remarkably decreased, when the hardness of the

tablet is increased and the disintegration thereof becomes worse). Actually, the tablets were not affected by the hardness thereof at all, and all the tablets show sufficiently rapid dissolution rate.

Pioglitazone HCl 15mg / Metformin HCl 500mg

Hardness (N)	126	170	232
dissolution rate after 30 min (%)			
Pioglitazone	102	103	102
Metformin	101	101	102

Pioglitazone HCl 15mg / Metformin HCl 850mg

Hardness (N)	178	218	297
dissolution rate after 30 min (%)			
Pioglitazone	102	102	101
Metformin	99	100	99

13. In sum, a median size of pioglitazone at 2-10 μm has enabled control of the blood concentration profile of a combination drug within a desired range, thereby achieving bioequivalence for both the pioglitazone and the metformin in the presently claimed combination drug. At the same time, reducing the particle size of pioglitazone to this range did not significantly affect the uniformity of either of the active pharmaceutical ingredients.

14. The ratio of the median size of metformin to that of the pioglitazone was held constant during the experiments above merely to illustrate the effect of micronization of the pioglitazone; but this should not be construed as an indication that the ratio is unimportant.

* * * * * *

15. I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 17th day of November, 2010.

Masahiko Koike

Masahiko Koike

Translation of Interview Form of ACTOS® Tablets

1-2 Dissolution

Pioglitazone hydrochloride is moderately soluble in N,N-dimethylformamide and methanol, slightly soluble in ethanol (99.5) and practically insoluble in water.

It is soluble in 0.1 mol/L HCl solution.

(The Japanese Pharmacopoeia 15th edition, Supplement II Practical Guide 2009, C-322 Hirokawa Shoten Co.)

2nd Table

■ Solubility in various pH ranges of solutions (20℃)

pH*	Solubility (mg/mL)	pH after dissolved
1.1	6.7	1.0
2.0	0.42	1.9
3.3	0.014	3.2
5.0	0.00026	4.9
7.0	0.000093	6.9
9.1	0.010	9.0
11.1	0.13	10.2
13.0	17	11.2

*pH 1.1: 0.1mol/L HCl, pH 2.0 - 11.1: Britton Robinson buffer
pH 13.0: 0.1mol/L NaOH

(Takeda Pharmaceutical Research Center)

ACTOS®
(pioglitazone hydrochloride) Tablets

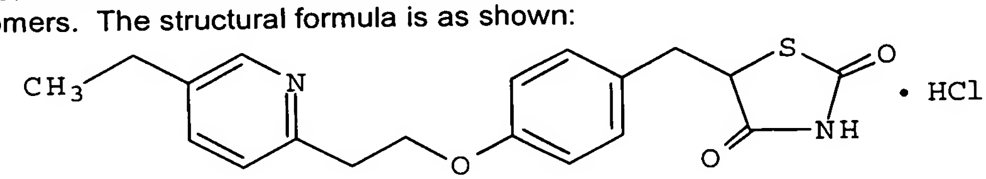
WARNING: CONGESTIVE HEART FAILURE

- Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients (see **WARNINGS**). After initiation of ACTOS, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered.
- ACTOS is not recommended in patients with symptomatic heart failure. Initiation of ACTOS in patients with established NYHA Class III or IV heart failure is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS**).

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus [NIDDM] or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α-glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert *in vivo*. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S{\cdot}HCl$ and a molecular weight of 392.90 daltons. It is soluble in *N,N*-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent agonist for peroxisome proliferator-activated receptor-gamma (PPARγ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPARγ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady-state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (> 99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (> 98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites

M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady-state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

In vitro data demonstrate that multiple CYP isoforms are involved in the metabolism of pioglitazone. The cytochrome P450 isoforms involved are CYP2C8 and, to a lesser degree, CYP3A4 with additional contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. *In vivo* studies of pioglitazone in combination with P450 inhibitors and substrates have been performed (see **Drug Interactions**). Urinary 6ß-hydroxycortisol/cortisol ratios measured in patients treated with ACTOS showed that pioglitazone is not a strong CYP3A4 enzyme inducer.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see **PRECAUTIONS**, <u>Hepatic Effects</u>).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS

improved glycemic control in both males and females. In controlled clinical trials, hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Drug-Drug Interactions
The following drugs were studied in healthy volunteers with a co-administration of ACTOS 45 mg once daily. Listed below are the results:

Oral Contraceptives: Co-administration of ACTOS (45 mg once daily) and an oral contraceptive (1 mg norethindrone plus 0.035 mg ethinyl estradiol once daily) for 21 days, resulted in 11% and 11-14% decrease in ethinyl estradiol AUC (0-24h) and C_{max} respectively. There were no significant changes in norethindrone AUC (0-24h) and C_{max}. In view of the high variability of ethinyl estradiol pharmacokinetics, the clinical significance of this finding is unknown.

Fexofenadine HCl: Co-administration of ACTOS for 7 days with 60 mg fexofenadine administered orally twice daily resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS had no significant effect on fexofenadine pharmacokinetics.

Glipizide: Co-administration of ACTOS and 5 mg glipizide administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: Co-administration of ACTOS with 0.25 mg digoxin administered orally once daily for 7 days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: Co-administration of ACTOS for 7 days with warfarin did not alter the steady-state pharmacokinetics of warfarin. ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: Co-administration of a single dose of metformin (1000 mg) and ACTOS after 7 days of ACTOS did not alter the pharmacokinetics of the single dose of metformin.

Midazolam: Administration of ACTOS for 15 days followed by a single 7.5 mg dose of midazolam syrup resulted in a 26% reduction in midazolam C_{max} and AUC.

Ranitidine HCl: Co-administration of ACTOS for 7 days with ranitidine administered orally twice daily for either 4 or 7 days resulted in no significant effect on pioglitazone pharmacokinetics. ACTOS showed no significant effect on ranitidine pharmacokinetics.

Nifedipine ER: Co-administration of ACTOS for 7 days with 30 mg nifedipine ER administered orally once daily for 4 days to male and female volunteers resulted in least square mean (90% CI) values for unchanged nifedipine of 0.83 (0.73 - 0.95) for C_{max} and 0.88 (0.80 - 0.96) for AUC. In view of the high variability of nifedipine

pharmacokinetics, the clinical significance of this finding is unknown.

Ketoconazole: Co-administration of ACTOS for 7 days with ketoconazole 200 mg administered twice daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 1.14 (1.06 - 1.23) for C_{max}, 1.34 (1.26 - 1.41) for AUC and 1.87 (1.71 - 2.04) for C_{min}.

Atorvastatin Calcium: Co-administration of ACTOS for 7 days with atorvastatin calcium (LIPITOR®) 80 mg once daily resulted in least square mean (90% CI) values for unchanged pioglitazone of 0.69 (0.57 - 0.85) for C_{max}, 0.76 (0.65 - 0.88) for AUC and 0.96 (0.87 - 1.05) for C_{min}. For unchanged atorvastatin the least square mean (90% CI) values were 0.77 (0.66 - 0.90) for C_{max}, 0.86 (0.78 - 0.94) for AUC and 0.92 (0.82 - 1.02) for C_{min}.

Theophylline: Co-administration of ACTOS for 7 days with theophylline 400 mg administered twice daily resulted in no change in the pharmacokinetics of either drug.

Cytochrome P450: See **PRECAUTIONS**

Gemfibrozil: Concomitant administration of gemfibrozil (oral 600 mg twice daily), an inhibitor of CYP2C8, with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 2 days prior with gemfibrozil (oral 600 mg twice daily) resulted in pioglitazone exposure (AUC_{0-24}) being 226% of the pioglitazone exposure in the absence of gemfibrozil (see **PRECAUTIONS**).[1]

Rifampin: Concomitant administration of rifampin (oral 600 mg once daily), an inducer of CYP2C8 with pioglitazone (oral 30 mg) in 10 healthy volunteers pre-treated for 5 days prior with rifampin (oral 600 mg once daily) resulted in a decrease in the AUC of pioglitazone by 54% (see **PRECAUTIONS**).[2]

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower plasma glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in

patients treated with ACTOS than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in patients treated with ACTOS compared to placebo (**Table 1**).

Table 1 Lipids in a 26-Week Placebo-Controlled Monotherapy Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (24 weeks and 16 weeks) and metformin (24 weeks and 16 weeks), the results were generally consistent with the data above. In placebo-controlled trials, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL in patients treated with ACTOS. A similar pattern of results was seen in 24-week combination therapy studies of ACTOS with sulfonylurea or metformin.

In a combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for patients treated with ACTOS was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed. A similar pattern of results was seen in a 24-week combination therapy study with ACTOS with insulin.

Clinical Studies

Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week, dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting plasma glucose (FPG) at endpoint compared to placebo (**Figure 1, Table 2**).

Figure 1 shows the time course for changes in FPG and HbA_{1c} for the entire study population in this 26-week study.

Figure 1 Mean Change from Baseline for FPG and HbA_{1c} in a 26-Week Placebo-Controlled Dose-Ranging Study

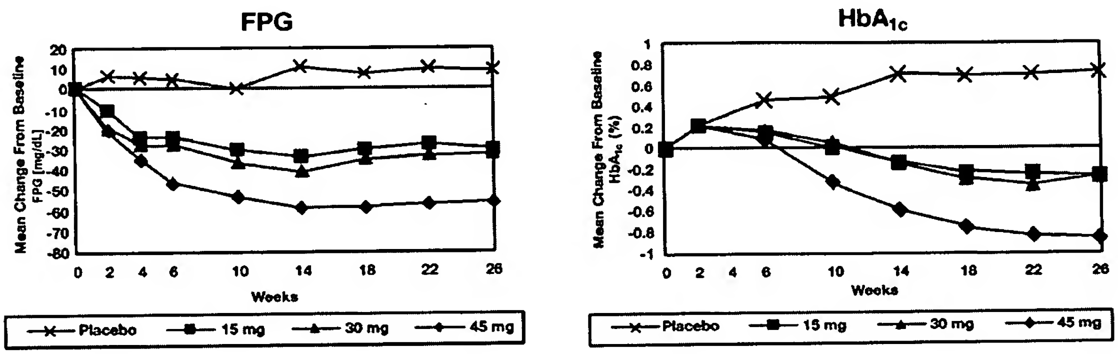


Table 2 shows HbA_{1c} and FPG values for the entire study population.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean⁺)	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean⁺)		-1.0*	-1.0*	-1.6*
FPG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean⁺)	9	-30	-32	-56
Difference from placebo (adjusted mean⁺)		-39*	-41*	-65*

⁺ Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously-treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FPG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous antidiabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FPG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FPG with ACTOS, in many cases the values did not return to

screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

Table 3 **Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study**

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FPG (mg/dL)	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FPG (mg/dL)	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week, placebo-controlled study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (**Table 4**).

Table 4 **Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study**

	Placebo	ACTOS 30 mg+ Once Daily	ACTOS 45 mg+ Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean++)	0.9	-0.6	-0.6
Difference from placebo (adjusted mean++)		-1.5*	-1.5*
FPG (mg/dL)	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean++)	18	-44	-50
Difference from placebo (adjusted mean++)		-62*	-68*

+ Final dose in forced titration

++ Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.2% and mean FPG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FPG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.7% and mean FPG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FPG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FPG at endpoint compared to placebo (**Table 5**).

Table 5 **Glycemic Parameters in a 16-Week Placebo-Controlled Study**

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean+)	0.8	-0.6
Difference from placebo (adjusted mean+)		-1.4*
FPG (mg/dL)	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean+)	8	-50
Difference from placebo (adjusted mean+)		-58*

+ Adjusted for baseline, pooled center, and pooled center by treatment interaction

* $p \leq 0.050$ vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.4% and mean FPG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FPG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FPG. At baseline, mean HbA_{1c} was 10.6% and mean FPG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FPG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FPG had not returned to screening levels by the end of the study.

Combination Therapy

Three 16-week, randomized, double-blind, placebo-controlled clinical studies and three 24-week, randomized, double-blind, dose-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled ($HbA_{1c} \geq 8\%$) despite current therapy with a sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

ACTOS Plus Sulfonylurea Studies

Two clinical studies were conducted with ACTOS in combination with a sulfonylurea. Both studies included patients with type 2 diabetes on a sulfonylurea, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 560 patients were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current sulfonylurea regimen. When compared to placebo at Week 16, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% and mean FPG by 39 mg/dL and 58 mg/dL for the 15 mg and 30 mg doses, respectively.

In the second study, 702 patients were randomized to receive 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current sulfonylurea regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.55% and 1.67% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 51.5 mg/dL and 56.1 mg/dL.

The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea.

ACTOS Plus Metformin Studies

Two clinical studies were conducted with ACTOS in combination with metformin. Both studies included patients with type 2 diabetes on metformin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 328 patients were randomized to receive either 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their current metformin regimen. When compared to placebo at Week 16, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FPG by 38 mg/dL.

In the second study, 827 patients were randomized to receive either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current metformin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 0.80% and 1.01% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 38.2 mg/dL and 50.7 mg/dL.

The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin.

ACTOS Plus Insulin Studies

Two clinical studies were conducted with ACTOS in combination with insulin. Both studies included patients with type 2 diabetes on insulin, either alone or in combination with another antidiabetic agent. All other antidiabetic agents were withdrawn prior to starting study treatment. In the first study, 566 patients receiving a median of 60.5 units per day of insulin were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily for 16 weeks in addition to their insulin regimen. When compared to placebo at Week 16, the addition of ACTOS to insulin significantly reduced both HbA_{1c} by 0.7% and 1.0% and FPG by 35 mg/dL and 49 mg/dL for the 15 mg and 30 mg dose, respectively.

In the second study, 690 patients receiving a median of 60.0 units per day of insulin received either 30 mg or 45 mg of ACTOS once daily for 24 weeks in addition to their current insulin regimen. The mean reductions from baseline at Week 24 in HbA_{1c} were 1.17% and 1.46% for the 30 mg and 45 mg doses, respectively. Mean reductions from baseline in FPG were 31.9 mg/dL and 45.8 mg/dL. Improved glycemic control was accompanied by mean decreases from baseline in insulin dose requirements of 6.0% and 9.4% per day for the 30 mg and 45 mg dose, respectively.

The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin.

INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

Initiation of ACTOS in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated (see **BOXED WARNING**).

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

WARNINGS

Cardiac Failure and Other Cardiac Effects

ACTOS, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. Patients should be observed for signs and symptoms of heart failure. If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered (see **BOXED WARNING**). Patients with NYHA Class III and IV cardiac status were not studied during pre-approval clinical trials and ACTOS is not recommended in these patients (see **BOXED WARNING** and **CONTRAINDICATIONS**).

In one 16-week, U.S. double-blind, placebo-controlled clinical trial involving 566 patients with type 2 diabetes, ACTOS at doses of 15 mg and 30 mg in combination with insulin was compared to insulin therapy alone. This trial included patients with long-standing diabetes and a high prevalence of pre-existing medical conditions as follows: arterial hypertension (57.2%), peripheral neuropathy (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (8.8%), vascular disease (6.4%), angina pectoris (4.4%), stroke and/or transient ischemic attack (4.1%), and congestive heart failure (2.3%).

In this study, two of the 191 patients receiving 15 mg ACTOS plus insulin (1.1%) and two of the 188 patients receiving 30 mg ACTOS plus insulin (1.1%) developed congestive heart failure compared with none of the 187 patients on insulin therapy alone. All four of these patients had previous histories of cardiovascular conditions including coronary artery disease, previous CABG procedures, and myocardial infarction. In a 24-week, dose-controlled study in which ACTOS was coadministered with insulin, 0.3% of patients (1/345) on 30 mg and 0.9% (3/345) of patients on 45 mg reported CHF as a serious adverse event.

Analysis of data from these studies did not identify specific factors that predict increased risk of congestive heart failure on combination therapy with insulin.

In type 2 diabetes and congestive heart failure (systolic dysfunction)

A 24-week post-marketing safety study was performed to compare ACTOS (n=262) to glyburide (n=256) in uncontrolled diabetic patients (mean HbA_{1c} 8.8% at baseline) with NYHA Class II and III heart failure and ejection fraction less than 40% (mean EF 30% at baseline). Over the course of the study, overnight hospitalization for congestive heart failure was reported in 9.9% of patients on ACTOS compared to 4.7% of patients on glyburide with a treatment difference observed from 6 weeks. This adverse event associated with ACTOS was more marked in patients using insulin at baseline and in patients over 64 years of age. No difference in cardiovascular mortality between the treatment groups was observed.

ACTOS should be initiated at the lowest approved dose if it is prescribed for patients with type 2 diabetes and systolic heart failure (NYHA Class II). If subsequent dose escalation is necessary, the dose should be increased gradually only after several months of treatment with careful monitoring for weight gain, edema, or signs and symptoms of CHF exacerbation.

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg once daily, or placebo (n=2633) (see **ADVERSE REACTIONS**). The percentage of patients who had

an event of serious heart failure was higher for patients treated with ACTOS (5.7%, n=149) than for patients treated with placebo (4.1%, n=108). The incidence of death subsequent to a report of serious heart failure was 1.5% (n=40) in patients treated with ACTOS and 1.4% (n=37) in placebo-treated patients. In patients treated with an insulin-containing regimen at baseline, the incidence of serious heart failure was 6.3% (n=54/864) with ACTOS and 5.2% (n=47/896) with placebo. For those patients treated with a sulfonylurea-containing regimen at baseline, the incidence of serious heart failure was 5.8% (n=94/1624) with ACTOS and 4.4% (n=71/1626) with placebo.

PRECAUTIONS

General

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Cardiovascular: In U.S. placebo-controlled clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, the incidence of serious cardiac adverse events related to volume expansion was not increased in patients treated with ACTOS as monotherapy or in combination with sulfonylureas or metformin vs. placebo-treated patients. In insulin combination studies, a small number of patients with a history of previously existing cardiac disease developed congestive heart failure when treated with ACTOS in combination with insulin (see **WARNINGS**). Patients with NYHA Class III and IV cardiac status were not studied in these ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

In postmarketing experience with ACTOS, cases of congestive heart failure have been reported in patients both with and without previously known heart disease.

Edema: ACTOS should be used with caution in patients with edema. In all U.S. clinical trials, edema was reported more frequently in patients treated with ACTOS than in placebo-treated patients and appears to be dose related (see **ADVERSE REACTIONS**). In postmarketing experience, reports of initiation or worsening of edema have been received. Since thiazolidinediones, including ACTOS, can cause fluid retention, which can exacerbate or lead to congestive heart failure, ACTOS should be used with caution in patients at risk for heart failure. Patients should be monitored for signs and symptoms of heart failure (see **BOXED WARNING**; **WARNINGS**, and **PRECAUTIONS**, **Information for Patients**).

Weight Gain: Dose related weight gain was seen with ACTOS alone and in combination with other hypoglycemic agents (**Table 6**). The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Table 6 — **Weight Changes (kg) from Baseline during Double-Blind Clinical Trials with ACTOS**

		Control Group (Placebo)	ACTOS 15 mg	ACTOS 30 mg	ACTOS 45 mg
		Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)	Median ($25^{th}/75^{th}$ percentile)
Monotherapy		-1.4 (-2.7/0.0) n=256	0.9(-0.5/3.4) n = 79	1.0(-0.9/3.4) n=188	2.6 (0.2/5.4) n = 79
Combination Therapy	Sulfonylurea	-0.5 (-1.8/0.7) n=187	2.0 (0.2/3.2) n=183	3.1 (1.1/5.4) n=528	4.1 (1.8/7.3) n=333
	Metformin	-1.4 (-3.2/0.3) n=160	N/A	0.9(-0.3/3.2) n=567	1.8(-0.9/5.0) n=407
	Insulin	0.2 (-1.4/1.4) n=182	2.3 (0.5/4.3) n=190	3.3 (0.9/6.3) n=522	4.1 (1.4/6.8) n=338

Note: Trial durations of 16 to 26 weeks

Ovulation: Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased plasma volume and have rarely been associated with any significant hematologic clinical effects (see **ADVERSE REACTIONS, Laboratory Abnormalities**).

Hepatic Effects: In pre-approval clinical studies worldwide, over 4500 subjects were treated with ACTOS. In U.S. clinical studies, over 4700 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels in the clinical studies.

During pre-approval placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) patients treated with ACTOS and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

In postmarketing experience with ACTOS, reports of hepatitis and of hepatic enzyme elevations to 3 or more times the upper limit of normal have been received. Very rarely, these reports have involved hepatic failure with and without fatal outcome, although causality has not been established.

Pending the availability of the results of additional large, long-term controlled clinical trials and additional postmarketing safety data, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes.

Serum ALT (alanine aminotransferase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgment pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation or continuation of therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

Macular Edema: Macular edema has been reported in post-marketing experience in diabetic patients who were taking pioglitazone or another thiazolidinedione. Some patients presented with blurred vision or decreased visual acuity, but some patients appear to have been diagnosed on routine ophthalmologic examination. Some patients had peripheral edema at the time macular edema was diagnosed. Some patients had improvement in their macular edema after discontinuation of their thiazolidinedione. It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Patients with diabetes should have regular eye exams by an ophthalmologist, per the Standards of Care of the American Diabetes Association. Additionally, any diabetic who reports any kind of visual symptom should be promptly referred to an ophthalmologist, regardless of the patient's underlying medications or other physical findings (see **ADVERSE REACTIONS**).

Fractures: In a randomized trial (PROactive) in patients with type 2 diabetes (mean duration of diabetes 9.5 years), an increased incidence of bone fracture was noted in female patients taking pioglitazone. During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for pioglitazone versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with pioglitazone 1.7% (30/1735) versus placebo 2.1% (37/1728). The risk of fracture should be considered in the care of patients, especially female patients, treated with pioglitazone and attention should be given to assessing and maintaining bone health according to current standards of care.

Macrovascular Outcomes:
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ACTOS or any other anti-diabetic drug.

Laboratory Tests
FPG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter per the clinical judgment of the health care professional (see **PRECAUTIONS, General,** Hepatic Effects and **ADVERSE REACTIONS, Serum Transaminase Levels**).

Information for Patients
It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients who experience an unusually rapid increase in weight or edema or who develop shortness of breath or other symptoms of heart failure while on ACTOS should immediately report these symptoms to their physician.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy and periodically thereafter per the clinical judgment of the health care professional. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

Therapy with ACTOS, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women. As a result, these patients may be at an increased risk for pregnancy while taking ACTOS. Thus, adequate contraception in premenopausal women should be recommended. This possible effect has not been investigated in clinical studies so the frequency of this occurrence is not known.

Drug Interactions
In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3A4 substrate (see **CLINICAL PHARMACOLOGY, Metabolism** and **Drug-Drug Interactions**).

An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats at oral doses

up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. In two 3-year studies in which pioglitazone was compared to placebo or glyburide, there were 16/3656 (0.44%) reports of bladder cancer in patients taking pioglitazone compared to 5/3679 (0.14%) in patients not taking pioglitazone. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were six (0.16%) cases on pioglitazone and two (0.05%) on placebo.

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an *in vitro* cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an *in vivo* micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rats, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of

10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers
Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breastfeeding woman.

Pediatric Use
Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use
Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

Over 8500 patients with type 2 diabetes have been treated with ACTOS in randomized, double-blind, controlled clinical trials. This includes 2605 high-risk patients with type 2 diabetes treated with ACTOS from the PROactive clinical trial. Over 6000 patients have been treated for 6 months or longer, and over 4500 patients for one year or longer. Over 3000 patients have received ACTOS for at least 2 years.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 7.

Table 7
Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency ≥ 5% of Patients Treated with ACTOS

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1

Pharyngitis	0.8	5.1

For most clinical adverse events the incidence was similar for groups treated with ACTOS monotherapy and those treated in combination with sulfonylureas, metformin, and insulin. There was an increase in the occurrence of edema in the patients treated with ACTOS and insulin compared to insulin alone.

In a 16-week, placebo-controlled ACTOS plus insulin trial (n=379), 10 patients treated with ACTOS plus insulin developed dyspnea and also, at some point during their therapy, developed either weight change or edema. Seven of these 10 patients received diuretics to treat these symptoms. This was not reported in the insulin plus placebo group.

The incidence of withdrawals from placebo-controlled clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

In controlled combination therapy studies with either a sulfonylurea or insulin, mild to moderate hypoglycemia, which appears to be dose related, was reported (see **PRECAUTIONS, General,** Hypoglycemia and **DOSAGE and ADMINISTRATION, Combination Therapy**).

In U.S. double-blind studies, anemia was reported in ≤ 2% of patients treated with ACTOS plus sulfonylurea, metformin or insulin (see **PRECAUTIONS, General,** Hematologic).

In monotherapy studies, edema was reported for 4.8% (with doses from 7.5 mg to 45 mg) of patients treated with ACTOS versus 1.2% of placebo-treated patients. In combination therapy studies, edema was reported for 7.2% of patients treated with ACTOS and sulfonylureas compared to 2.1% of patients on sulfonylureas alone. In combination therapy studies with metformin, edema was reported in 6.0% of patients on combination therapy compared to 2.5% of patients on metformin alone. In combination therapy studies with insulin, edema was reported in 15.3% of patients on combination therapy compared to 7.0% of patients on insulin alone. Most of these events were considered mild or moderate in intensity (see **PRECAUTIONS, General,** Edema).

In one 16-week clinical trial of insulin plus ACTOS combination therapy, more patients developed congestive heart failure on combination therapy (1.1%) compared to none on insulin alone (see **WARNINGS, Cardiac Failure and Other Cardiac Effects**).

Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive)

In PROactive, 5238 patients with type 2 diabetes and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg daily or placebo (n=2633) in addition to standard of care. Almost all subjects (95%) were receiving cardiovascular medications (beta blockers, ACE inhibitors, ARBs, calcium channel blockers, nitrates, diuretics, aspirin, statins, fibrates). Patients had a mean age of 61.8 years, mean duration of diabetes 9.5 years, and mean HbA1c 8.1%. Average duration of follow-up was 34.5 months. The primary objective of this trial was to examine the effect of ACTOS on mortality and macrovascular morbidity in patients with type 2 diabetes mellitus who were at high risk for macrovascular events. The primary efficacy variable was the time to the first occurrence of any event in the cardiovascular composite endpoint (see table 8 below). Although there was no statistically significant difference between ACTOS and placebo for the 3-year

incidence of a first event within this composite, there was no increase in mortality or in total macrovascular events with ACTOS.

Table 8

Number of First and Total Events for Each Component within the Cardiovascular Composite Endpoint				
	Placebo N=2633		**ACTOS N=2605**	
Cardiovascular Events	First Events (N)	Total events (N)	First Events (N)	Total events (N)
Any event	572	900	514	803
All-cause mortality	122	186	110	177
Non-fatal MI	118	157	105	131
Stroke	96	119	76	92
ACS	63	78	42	65
Cardiac intervention	101	240	101	195
Major leg amputation	15	28	9	28
Leg revascularization	57	92	71	115

Postmarketing reports of new onset or worsening diabetic macular edema with decreased visual acuity have also been received (see **PRECAUTIONS, General,** Macular Edema).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. The fall in hemoglobin and hematocrit with ACTOS appears to be dose related. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in patients treated with ACTOS. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have rarely been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During all clinical studies in the U.S., 14 of 4780 (0.30%) patients treated with ACTOS had ALT values ≥ 3 times the upper limit of normal during treatment. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.9% of patients treated with ACTOS were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see **PRECAUTIONS, General,** Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. An isolated elevation to greater than 10 times the upper limit of normal was noted in 9 patients (values of 2150 to 11400 IU/L). Six of these patients continued to receive ACTOS, two patients had completed receiving study medication at the time of the elevated value and one patient discontinued study medication due to the elevation. These elevations

resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c} which is a better indicator of long-term glycemic control than FPG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates. After initiation of ACTOS or with dose increase, patients should be carefully monitored for adverse events related to fluid retention (see **BOXED WARNING** and **WARNINGS**).

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose

The dose of ACTOS should not exceed 45 mg once daily in monotherapy or in combination with sulfonylurea, metformin, or insulin.

Dose adjustment in patients with renal insufficiency is not recommended (see **CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism**).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see **PRECAUTIONS, General,** Hepatic Effects and **CLINICAL PHARMACOLOGY, Special Populations,** Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see **PRECAUTIONS, General,** Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:
NDC 64764-151-04 Bottles of 30
NDC 64764-151-05 Bottles of 90
NDC 64764-151-06 Bottles of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "30" on the other, available in:
NDC 64764-301-14 Bottles of 30
NDC 64764-301-15 Bottles of 90
NDC 64764-301-16 Bottles of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:
NDC 64764-451-24 Bottles of 30
NDC 64764-451-25 Bottles of 90
NDC 64764-451-26 Bottles of 500

STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

REFERENCES

1. Deng, LJ, et al. Effect of gemfibrozil on the pharmacokinetics of pioglitazone. *Eur J Clin Pharmacol* 2005; 61: 831-836, Table 1.
2. Jaakkola, T, et al. Effect of rifampicin on the pharmacokinetics of pioglitazone. *Clin Pharmacol Brit Jour* 2006; 61:1 70-78.

Rx only

Manufactured by:
Takeda Pharmaceutical Company Limited

Osaka, Japan

Marketed by:
Takeda Pharmaceuticals America, Inc.
One Takeda Parkway
Deerfield, IL 60015

05-1150 August 2008

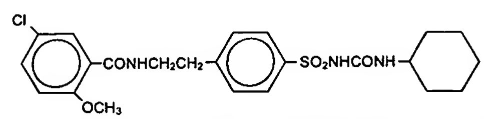
Diaßeta® (glyburide) Tablets USP
1.25, 2.5 and 5 mg

DESCRIPTION

Diaßeta® (glyburide) is an oral blood-glucose-lowering drug of the sulfonylurea class. It is a white, crystalline compound, formulated as tablets of 1.25 mg, 2.5 mg, and 5 mg strengths for oral administration. Diaßeta tablets USP contain the active ingredient glyburide and the following inactive ingredients: dibasic calcium phosphate USP, magnesium stearate NF, microcrystalline cellulose NF, sodium alginate NF, talc USP. Diaßeta 1.25 mg tablets USP also contain D&C Yellow #10 Aluminum Lake and FD&C Red #40 Aluminum Lake. Diaßeta 2.5 mg tablets USP also contain FD&C Red #40 Aluminum Lake. Diaßeta 5 mg tablets USP also contain D&C Yellow #10 Aluminum Lake, and FD&C Blue #1. Chemically, Diaßeta is identified as 1-[[p-[2-(5-Chloro-o-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea.

The CAS Registry Number is 10238-21-8.

The structural formula is:



The molecular weight is 493.99. The aqueous solubility of Diaßeta increases with pH as a result of salt formation.

CLINICAL PHARMACOLOGY

Diaßeta appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which Diaßeta lowers blood glucose during long-term administration has not been clearly established.

With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

In addition to its blood glucose lowering actions, Diaßeta produces a mild diuresis by enhancement of renal free water clearance. Clinical experience to date indicates an extremely low incidence of disulfiram-like reactions in patients while taking Diaßeta.

Pharmacokinetics

Single-dose studies with Diaßeta in normal subjects demonstrate significant absorption within one hour, peak drug levels at about four hours, and low but detectable levels at twenty-four hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple-dose studies with Diaßeta in diabetic patients demonstrate drug level concentration-time curves similar to single-dose studies, indicating no build-up of drug in tissue depots. The decrease of glyburide in the serum of normal healthy individuals is biphasic, the terminal half-life being about 10 hours. In

single-dose studies in fasting normal subjects, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning doses in non-fasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A one-year study of diabetic patients treated with Diaßeta showed no reliable correlation between administered dose and serum drug level.

The major metabolite of Diaßeta is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites contribute no significant hypoglycemic action since they are only weakly active (1/400th and 1/40th, respectively, as glyburide) in rabbits.

Diaßeta is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by Diaßeta is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding Diaßeta. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with Diaßeta in clinical use.

INDICATIONS AND USAGE

Diaßeta is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

Diaßeta is contraindicated in patients:

1. With known hypersensitivity to the drug or any of its excipients.
2. With type 1 diabetes mellitus or diabetic ketoacidosis, with or without coma. These conditions should be treated with insulin.
3. Treated with bosentan.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in

patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes 19 (supp. 2): 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of Diaßeta and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

Persons allergic to other sulfonamide derivatives may develop an allergic reaction to glyburide as well.

PRECAUTIONS

General

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Diaßeta or any other anti-diabetic drug.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Severe renal or hepatic insufficiency may cause elevated blood levels of Diaßeta and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious, prolonged hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in patients with autonomic neuropathy, the elderly, and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents.

Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used. Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue Diaßeta and administer insulin.

The effectiveness of any oral hypoglycemic drug, including Diaßeta, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This

phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

Hemolytic Anemia: Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. Because Diaßeta belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD deficiency and a non-sulfonylurea alternative should be considered. In postmarketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

Information for Patients

Patients should be informed of the potential risks and advantages of Diaßeta and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Laboratory Tests

Periodic fasting blood glucose measurements should be performed to monitor therapeutic response. A glycosylated hemoglobin determination should also be performed periodically.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, ACE inhibitors, disopyramide, fluoxetine, clarithromycin, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving Diaßeta, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving Diaßeta, the patient should be observed closely for loss of control.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

A possible interaction between glyburide and fluoroquinolone antibiotics has been reported resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism for this interaction is not known.

Possible interactions between glyburide and coumarin derivatives have been reported that may either potentiate or weaken the effects of coumarin derivatives. The mechanism of these interactions is not known.

Rifampin may worsen glucose control of glyburide because rifampin can significantly induce metabolic isozymes of glyburide such as CYP2C9 and 3A4.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Diaßeta, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving Diaßeta, the patient should be observed closely for hypoglycemia.

An increased incidence of elevated liver enzymes was observed in patients receiving glyburide concomitantly with bosentan. Therefore this combination should not be used. (See CONTRAINDICATIONS.)

Diaßeta may increase cyclosporine plasma concentration and potentially lead to its increased toxicity. Monitoring and dosage adjustment of cyclosporine are therefore recommended when both drugs are coadministered.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Diaßeta is non-mutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay. Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects.

No drug related effects were noted in any of the criteria evaluated in the two year oncogenicity study of glyburide in mice.

Pregnancy

Teratogenic Effects: Pregnancy Category C
Diaßeta has been shown to affect the maturation of the long bones (humerus and femur) in rat pups when given in doses 6250 times the maximum recommended human dose. These effects, which were seen during the period of lactation and not during organogenesis, are a shortening of the bones with effects to various structures of the long bones, especially in humerus and femur.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Diaßeta should be used during pregnancy only if the potential benefit justifies the risk to the fetus. Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If Diaßeta is used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers

Although it is not known whether Diaßeta is excreted in human milk, some sulfonylureas are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants

may exist, a decision should be made whether to discontinue nursing or to discontinue administering the drug, taking into account the importance of the drug to the mother. If Diaßeta is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In US clinical studies of glyburide, 1406 of 2897 patients were ≥60 years and 515 patients were ≥70 years. Differences in safety and efficacy were not determined between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients are particularly susceptible to hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly (see PRECAUTIONS). The initial and maintenance dosing should be conservative to avoid hypoglycemic reactions.

In three published studies of 20 to 51 subjects each, mixed results were seen in comparing the pharmacokinetics of glyburide in elderly versus younger subjects. However, observed pharmacodynamic differences indicate the necessity for dosage titration to a specified therapeutic response.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs or other sympatholytic agents. (See PRECAUTIONS, General; and DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE Sections.

Gastrointestinal Reactions: Cholestatic jaundice and hepatitis may occur rarely which may progress to liver failure; Diaßeta should be discontinued if this occurs. Liver function abnormalities, including isolated transaminase elevations, have been reported. Gastrointestinal disturbances, e.g., nausea, epigastric fullness, and heartburn, are the most common reactions and occur in 1.8% of treated patients. They tend to be dose-related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in 1.5% of treated patients. These may be

transient and may disappear despite continued use of Diaßeta; if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, which occasionally may present as purpura, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions: Hepatic porphyria reactions have been reported with sulfonylureas; however, these have not been reported with Diaßeta. Disulfiram-like reactions have been reported very rarely with Diaßeta. Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions: Changes in accommodation and/or blurred vision have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia and vasculitis have been reported.

OVERDOSAGE

Overdosage of sulfonylureas, including Diaßeta, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with Diaßeta or any other hypoglycemic agent. The patient's fasting blood glucose must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Periodic glycosylated hemoglobin determinations should be performed.

Short-term administration of Diaßeta may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

1. **Usual Starting Dose**

The usual starting dose of Diaßeta as initial therapy is 2.5 to 5 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1.25 mg daily. (See PRECAUTIONS Section for patients at increased risk). Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Transfer of patients from other oral antidiabetic regimens to Diaßeta should be done conservatively and the initial daily dose should be 2.5 to 5 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide, to Diaßeta, no transition period and no initial priming dose is necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first two weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Bioavailability studies have demonstrated that Glynase®* PresTab®* Tablets 3 mg are not bioequivalent to Diaßeta Tablets USP 5 mg. Therefore, these products are not substitutable and patients should be retitrated if transferred.

Some Type II diabetic patients being treated with insulin may respond satisfactorily to Diaßeta. If the insulin dose is less than 20 units daily, substitution of Diaßeta 2.5 to 5 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on Diaßeta 5 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to Diaßeta. In these patients, insulin dosage is decreased by 50% and Diaßeta 5 mg daily is started. Please refer to Usual Maintenance Dose for further explanation.

2. **Usual Maintenance Dose**

The usual maintenance dose is in the range of 1.25 to 20 mg daily, which may be given as a single dose or in divided doses (See Dosage Interval Section). Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between Diaßeta and the other oral hypoglycemic agents. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 5 mg of Diaßeta should be observed. A maintenance dose of 5 mg Diaßeta provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of Diaßeta 5 mg concomitantly with a 50% reduction in insulin

dose. Progressive withdrawal of insulin and increase of Diaßeta in increments of 1.25 to 2.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and Diaßeta are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should self-test their blood for glucose and their urine for acetone at least 3 times daily and report results to their physician. Self-testing of urinary glucose is a less desirable alternative. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

3. **Maximum Dose**
   Daily doses of more than 20 mg are not recommended.

4. **Dosage Interval**
   Once-a-day therapy is usually satisfactory, based upon usual meal patterns and a 10 hour half-life of Diaßeta. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See PRECAUTIONS Section.)

HOW SUPPLIED

Diaßeta (glyburide) tablets USP are available in the following strengths and package sizes:

1.25 mg (peach, capsule-shaped, flat faced, beveled edge tablet debossed "Dia ß" with a score line between the "Dia" and the "ß" on one side and plain on the other side).

Bottles of 50	(NDC 0039-0053-05)

2.5 mg (pink, capsule-shaped, flat faced, beveled edge tablet debossed "Dia ß" with a score line between the "Dia" and "ß" on one side and plain on the other side).

Bottles of 100	(NDC 0039-0051-10)
Bottles of 500	(NDC 0039-0051-50)

5 mg (green, capsule-shaped, flat faced, beveled edge tablet debossed "Dia ß" with a score line between the "Dia" and "ß" on one side and plain on the other side).

Bottles of 100	(NDC 0039-0052-10)
Bottles of 500	(NDC 0039-0052-50)
Bottles of 1000	(NDC 0039-0052-70)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

Dispense in well-closed containers with safety closures.

Rx only

Revised XXXXXX

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Biorelevant dissolution media as a predictive tool for glyburide a class II drug

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ABSTRACT

The purpose of this study was to predict the oral absorption of glyburide. Biorelevant dissolution methods, combined with permeability measurements and computational simulations, were used to predict the oral absorption of glyburide. The objective was to establish *in vitro/in vivo* correlations (IVIVCs) based on the biopharmaceutics drug classification system. The solubility of the glyburide powder was measured in different media. The dissolution behavior of two commercial tablet formulations was tested in different media. Two chemical grades of sodium taurocholate: low quality (LQ) = crude and high quality (HQ) = 97% purity, and egg-lecithin: LQ = 60% and HQ = 99.1% purity were used to prepare fasted state small intestinal fluid (FaSSIF). Simulated intestinal fluid (SIF) and blank FaSSIF without lecithin and taurocholate (BL-FaSSIF) were used as controls. The dissolution tests were performed under constant pH and dynamic pH conditions. The dynamic pH range from 5.0 to 7.5 simulated the biological pH range of gastrointestinal (GI) tract in the fasted state. The drug permeability was studied using Caco-2 cell line. The predictions of the fraction dose absorbed were performed using GastroPlus™. The results of the simulations were compared with actual clinical data taken from a bioequivalence study. The solubility of glyburide was highest in LQ-FaSSIF. The two tablet formulations had significantly different dissolution behaviors in LQ-FaSSIF. The *in vitro* data was used as the input function into a simulation software. The dynamic LQ-FaSSIF dissolution data achieved the best prediction of the average AUC and C_{max} of the clinically observed data. The present study shows that BCS based parameters combined with software simulations can be used to establish an IVIVC for glyburide. *In vitro/in silico* tools can potentially be used as surrogate for bioequivalence studies.

1. Introduction

Oral dosage forms are the most common formulations because of their convenient administration and their economy of manufacture (Goodman et al., 1999). In order to successfully develop an oral product, formulation scientists have to investigate the physicochemical properties of all potential drug candidates. These properties include but are not limited to solubility, bulk density, pK_a, crystallinity, osmolality, pH, X-ray diffraction, IR spectra, density, particle size and surface area. High throughput *in vitro* technologies are commonly used for such screenings (Parrott and Lavé, 2002). These methodologies are optimized to characterize one characteristic at a time. The disadvantage of such specialized tests is that they, use artificial test conditions which might not reflect the drugs behavior in a biological environment. This is especially important for

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poorly soluble drugs. The *in vivo* performance and bioavailability of drugs must be studied in patients in order to ensure efficacy and safety. Due to the time consuming procedure and the high costs of clinical studies, *in vitro* and *in vivo* correlations (IVIVCs) are highly desirable to predict the *in vivo* performance of dosage forms (Vogelpoel et al., 2004). Therefore, the development of more universal *in vitro* methods that can be used to estimate the *in vivo* performance of a potential drug product in an early stage of the development process is highly desirable.

A mechanistic approach to the oral drug absorption was developed by Amidon et al. (1995) and is known as the biopharmaceutics drug classification system (BCS). It defined two fundamental parameters: solubility and permeability. Both are the key variables in governing the rate and extent of oral drug absorption. Based on the theory of the BCS and the physiology of the gastrointestinal (GI) tract, a mathematical model was developed called the Compartmental Absorption and Transit (CAT) model (Yu et al., 1996b). The CAT model can be used to predict the oral absorption of drugs. Compared to traditional models, such as the Single-Tank mixing model (Sinko et al., 1991) or the macroscopic mass balance (Oh et al., 1993), the CAT model adopted the physiological GI conditions much better (Yu et al., 1996a). However, the CAT model does not consider any absorption in the stomach or the colon. A new model called the Advanced Compartmental Absorption and Transit model (ACAT) was developed by Simulations Plus Inc. and is available under the name GastroPlus™. The ACAT model includes more physicochemical and physiological factors, and accounts for the absorption in stomach and colon (GastroPlus™ Manual, 2004).

In order to predict the oral drug absorption the software requires certain input parameters. Such parameters should reflect the *in vivo* conditions and include solubility and permeability. For poorly soluble drugs, the dissolution might be directly influenced by the solubility of the drug substances in the intestinal juices. If the permeability of a poorly soluble drug is high, its *in vivo* dissolution behavior might be the limiting/controlling factor of drug absorption (Galia et al., 1998). Therefore, for computer simulations it is important to develop *in vitro* dissolution methods that can simulate the *in vivo* dissolution behavior.

In vitro dissolution tests are standard methods accepted by regulatory agencies to assess the biopharmaceutical quality of drug products (Löbenberg et al., 2000). Drug release tests are routinely used in the pharmaceutical industry for quality control and drug development (Costa and Lobo, 2001). Pharmacopoeias like the USP, list several different dissolution apparatuses such as the basket, the paddle, and the reciprocating cylinder or flow through cell. The basket and paddle apparatus is routinely used because of its easy handling (Löbenberg et al., 2000). The simulation of the *in vivo* dissolution in such an apparatus is challenging because it may only simulate one condition at a time. For example, it may only simulate the gastric environment separately from the others. However, to be able to simulate the *in vivo* dissolution behavior changing environments are needed. The development of suitable dissolution media with changing environmental conditions is a critical issue, especially for the poorly soluble drugs. There are various dissolution media described in the national pharmacopoeias including simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) (USP 29). These media act as buffers that cover the physiological pH range from 1.2 to 6.8 (Löbenberg and Amidon, 2000). For many poorly soluble drugs, the *in vitro* dissolution in such media will not produce useful information because pH is not the only factor which influences solubility and drug release (Jinno et al., 2000). The modifications evident in dissolution media such as adding surfactants (Löbenberg and Amidon, 2000) or using emulsion or organic solvent were investigated in the past (El-Massik et al., 1996). But these modified media might not truly reflect *in vivo* conditions. In order to improve *in vitro/in vivo* conditions, the dissolution media should mimic the physiological environment of the GI tract (Galia et al., 1998). New biorelevant dissolution media (BDM) were developed and published in the 1995 FIP guidance: fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF). They contain bile salts (sodium taurocholate) and lecithin to simulate the physiological environment in the GI tract (Dressman et al., 1998). The advantage of using these media is that they might simulate the *in vivo* dissolution. The *in vitro* dissolution can then be used to predict the oral drug absorption (Löbenberg et al., 2000).

Glyburide is a second-generation sulfonylurea. It is orally used as an hypoglycemic agent to treat non-insulin-dependent (type II) diabetes mellitus (Pearson, 1985; Neuvonen and Kivisto, 1991). The aqueous solubility of the glyburide is low, and highly pH-dependent in the physiological range due to its pK_a of 5.3 (Löbenberg et al., 2000). Previous studies have demonstrated that the oral absorption of the glyburide is formulation-dependent (Neugebauer et al., 1985). Blume et al. (1993) had shown that the dissolution behaviors of different formulations play an important role in the oral performance and the bioavailability of this drug.

In this study, we investigated two commercial glyburide formulations. Since the glyburide should be administered before a meal to obtain sufficient pharmacokinetic profiles, we only investigated the fasted state medium FaSSIF (Otoom et al., 2001; Euglucon N. Rote Liste, 2005). The research presented in this paper focusses on the dissolution behavior of glyburide formulations in the FaSSIF of different chemical purities. The dissolution behaviors in other media including simulated intestinal fluid and the blank-FaSSIF without bile salts and lethicin were also studied as controls. The obtained *in vitro* dissolution profiles were used as input function, in GastroPlus™ to predict the oral absorption. The establishment of *in vivo/in vitro* correlations (IVIVCs) is discussed.

2. Material and methods

2.1. *Chemicals*

Sodium taurocholate crude (low quality: LQ) and 97% pure (high quality: HQ) were purchased from Sigma–Aldrich (USA). Egg-lecithin 60% (LQ) was purchased from ICN (USA). Egg-phospharidylcholine, Lipoid E PC 99.1% pure (HQ) was a gift from Lipoid GmbH (Ludwigshafen, Germany). Potassium dihydrogen phosphate, potassium chloride, sodium chloride, sodium hydroxide, phosphoric acid and hydrochloride acid (analytical grade) were purchased from BDH (USA).

Two 3.5 mg glyburide tablets were used as follows: Euglucon N® 3.5 mg tablets as reference product (Lot# 01N400, Boehringer Mannheim/Hoechs, Germany) and Glukovital® 3.5 mg tablet as test product (Lot# 09601, Dr. August Wolff Arzneimittel, Bielefeld, Germany).

Dulbecco's Modified Eagle's Medium (DMEM), L-glutamine, transferrin, trypsin-EDTA and HEPES were purchased from the GIBCO BRL Co. Fetal bovine serum (FBS), sodium pyruvate and Hank's solution were obtained from Sigma (MO, USA). PBS contains 140 mM NaCl, 260 mM KCl, 8.1 mM Na_2HPO_4, 1.47 mM KH_2PO_4, pH 7.2. The Hank's solution with 10 mM MES or HEPES adjusted the pH to 6.5 or 7.4 using 0.1N HCl or 0.2N NaOH, respectively. The resulting solution was used as a transport medium in the permeability study. Transwell® inserts (24.5 mm, pore size 0.4 μm, 4.7 cm^2, Corning Costar) were used for the Caco-2 cell monolayer culture and transport experiments. Cell culture flasks (75 cm^2) were used for the normal cell culture experiments. Both were obtained from Corning Costar (USA).

2.2. *Preparation of dissolution media*

The composition of the simulated intestinal fluid was the same as USP 28 without pancreatin. Fasted state simulating intestinal fluids was made from two chemical grades (LQ and HQ) of sodium taurocholate and lecithin. The FaSSIF contains 3 mM sodium taurocholate and 0.75 mM lethicin (Galia et al., 1998). The blank of FaSSIF (BL-FaSSIF) had the same composition as FaSSIF but did not contain lecithin or sodium taurocholate.

2.3. *Solubility of glyburide in different media*

Twenty milligrams (excess) glyburide powder (Lot# N326, Hoechst AG, Frankfurt, Germany) was added into 10 mL of different dissolution media (two chemical grades of FaSSIF, SIF and BL-FaSSIF) at pH 1.7, 5.0, 6.5, 7.4 values and stirred overnight (12 h) at 37 ± 0.5 °C water bath. The pH of each sample was checked during the experiment time. The resulting solution was then filtered through a 0.22 μm Millipore membrane filter. The filter membrane was checked for adsorption and no adsorption was detected.

2.4. *In vitro dissolution studies at pH 6.5*

A USP dissolution apparatus II (DT 6 Erweka, Germany) was used for all dissolution studies. The dissolution test was carried out at 37 ± 0.5 °C in 900 mL dissolution media at 75 rpm. The samples were withdrawn using a 10 mL syringe (B-D, USA) assembled with the steel tube and 10 μm filter (Lot# 31119B, Varian, USA). At each sampling time, a 5 mL sample was withdrawn and a 5 mL blank medium (preheated at 37 ± 0.5 °C) was added back into the vessels.

2.5. *Dynamic dissolution studies*

The dissolution apparatus and conditions were the same as previously described. The pH of the dissolution media was changed during the experiment. Five pH values were selected, 6.0, 6.5, 7.0, 7.5 and 5.0 corresponding to the physiological environment in the duodenum, jejunum, ileum and colon, respectively. The pH change was adapted to the pH changes 5 used by GastroPlus™ software. Samples were taken at 30, 90, 150, 210 and 270 min. At the end of each time interval, the pH was changed using concentrated sodium hydroxide or phosphoric acid. A pH meter (Digital 109, Corning, USA) was used to monitor the adjustment to the desired pH value.

2.6. *Permeability determination*

Caco-2 cells (passages 36–45, ATCC, Rockville, MD, USA) were maintained at 37 °C in Dulbeco's Modified Eagle's Medium with 4.5 g/L glucose, 1 mM sodium pyruvate, 10% (v/v) fetal bovine serum, 10 μg/mL human transferrin and 4.8 mg/mL HEPES, in an atmosphere of 5% CO_2 and 90% relative humidity. A total of 50,000 cells/cm^2 in medium were seeded in each apical chamber of Transwell® inserts. Three milliliters of medium was transferred in the basal receiving side.

The integrity and permeability of the cell monolayer was determined by electrical resistance measurements (VOHM, World Precision Inc., USA). The transepithelial electrical resistance values obtained in the absence of cells was considered as background measurements. The transport experiment was started based on the TEER of the monolayer when it reached 400 Ω cm^2 or higher. This is typically the case after 18–23 days after seeding cells on the transwell inserts. Lucifer yellow was used as a paracellular quality control marker, its effective permeability coefficient (P_{eff}) should be less than 2×10^{-7} cm/s. Lucifer yellow was measured by 485 nm excitation and 530 nm emission using a spectrofluorometer (model: FLUOROMAX, SPEX Industries Inc., USA). Glyburide (20 μM) was dissolved in the transport medium (1.5 mL) and was carefully added to the apical surface. Three milliliters of blank transport medium was added to basal receiving side. The cells were incubated at 37 °C in an atmosphere of 95% humidity; the concentration of the glyburide in both chambers was analyzed by HPLC at predetermined time intervals. In order to maintain the sink condition, the inserts were moved to the pre-prepared wells that contained fresh transport medium at predetermined time intervals. After each experiment, the TEER values were measured in all inserts and the integrity of the cell monolayer was confirmed.

The effective permeability coefficient (P_{eff}) was calculated using the following Eq. (1):

$$P_{eff} = \frac{V}{A \times C_o} \times \frac{dc}{dt}\,(\text{cm/s}) \tag{1}$$

where dc/dt, the flux across the monolayer (mM/s), is the initial slope of a plot of the cumulative receiver concentration versus time; V the volume of the receiver chamber (mL); A the surface area of the monolayer (cm^2), which is 4.7 cm^2 for the transwell insert in this experiment; and C_o is the initial concentration (mM) in the donor compartment.

2.7. *HPLC analysis*

Sample analysis was achieved by HPLC. The HPLC system consisted of an automatic sample injector (SIL-9A, Shimadzu, Japan), a pump (LC-60, Shimadzu, Japan), a UV detector (SPD-

6AV, Shimadzu, Japan) and an analytical column LiChoCART 125-4 LiChospher 60 Rp-select B (5 μm, Merck, Darmstadt, Germany) with a guard column. The samples were centrifuged at 12,000 rpm for 15 min using an Eppendorf centrifuge (Model 5415, Brinkmann, Germany). Thirty microliters of supernatant was directly injected into the HPLC system. The mobile phase consisted of a mixture of the acetonitrile and (25 mM, pH 4.5) sodium dihydrogen phosphate buffer. The percentage of the acetonitrile in the mobile phase was between 42 and 45% base on the separation of the impurities in the sample matrixes. The drug, glyburide was detected at a wavelength of 230 nm and the retention time was between 5 and 8 min depending on the organic ratio in the mobile phase. Samples were stable during the analytical time. An integrator (C-R3A, Shimadzu, Japan) was used for peak integration. Analysis of the dissolution and cell culture samples used the same HPLC condition.

2.8. Computer simulations

GastroPlus™ (Version 4.0.0005, Simulations Plus Inc., USA) was used to simulate the absorption and pharmacokinetics of the reference and test formulations. The program has three input pages: compound, physiology and pharmacokinetics, respectively. In the compound page, basic data of the drug's physical and chemical properties such as bulk density, solubility, dose, pK_a and particle radius are entered. Our values were taken from the manufacturer's certificate of analysis, literature or it was estimated using computer software (Reynolds, 1993; Budavari and O'Neil, 1996). The human permeability (P_{eff}) of glyburide was estimated using Caco-2 data (see Section 2.6). The solubility–pH profiles of glyburide were obtained as described in the previous section. The $\log P$ of glyburide was calculated by the KowWin software online-software on the Internet (Syracuse, 2004). The diffusion coefficient of glyburide was estimated by GastroPlus™.

The *in vitro* dissolution profiles of glyburide tablets were used as input functions into GastroPlus™ using the "tabulated *in vitro* data" function. The drug release profiles were used by the software to calculate the drug concentration in each compartment. The estimated human permeability data were computed using the human fasted $\log D$ absorption model to account for permeability. The *in silico* gut (GastroPlus™) then calculates the fraction dose absorbed based on the ACAT model using drug concentration, permeability, surface area and transit time in each compartment. Pharmacokinetic parameters, e.g. volume of distribution, clearance and microconstants can be added to the software in the pharmacokinetic page, which enables the software to calculate plasma concentration–time curves.

In the physiology page, the default values for transit time were selected for each compartment.

The clinical data for both formulations were obtained from bioequivalence study and all data were made available to us (Blume and Mutschler, 1989). The pharmacokinetic data were calculated using the software Kinetica 2000 (InnaPhase Corporation, USA). The Micro-Extravascular model fitting model was selected to calculate pharmacokinetic parameters. The mean values of the clinical data from 15 healthy volunteers for both formulations fitted well in a two-compartmental model (Rydberg et al., 1997). The pharmacokinetic parameters, such as clearance, volume of distribution, K_{12}, K_{21}, etc., were used for the simulations using GastroPlus™.

2.9. Statistics

Release profiles comparison: the difference factor (f_1, Eq. (2)) and similarity factor (f_2, Eq. (3)) were used to compare the drug release profiles. The equations are as below (Costa and Lobo, 2001):

$$f_1 = \frac{\sum_{j=1}^{n}|R_j - T_j|}{\sum_{j=1}^{n}R_j} \times 100 \tag{2}$$

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n}|R_j - T_j|^2\right]^{-0.5} \times 100\right\} \tag{3}$$

where n is the sample number, and R_j and T_j are the percentages of the reference and test drug release, respectively, at different time intervals j. The f_1 value increases proportionally due to the dissimilarity between the two dissolution profiles. If f_2 of two dissolution drug release profiles is between 50 and 100, then these two drug release profiles are similar. Value under 50 indicates differences between the release profiles (Costa and Lobo, 2001).

Percent prediction error (%PE) was calculated using Eq. (4) (Guidance for Industry: FDA, 1997).

$$\%PE = \frac{\text{observed} - \text{predicted}}{\text{observed}} \times 100 \tag{4}$$

Liner regression: the linear regression for the observed and simulated data was performed using MS Office Excel (2000). The 95% confident interval was applied for analysis of linear regression.

Significance of differences between experiments was calculated by paired two-sample for means t-test in MS Office Excel (2000). In all cases, statistical significance was calculated at $p < 0.05$ level.

3. Results and discussion

3.1. Solubility of glyburide in different media

Glyburide (pK_a 5.3) is a weak acid with poor aqueous solubility (El-Massik et al., 1996). The solubility of glyburide powder was measured in four different media including BL-FaSSIF, SIF, HQ-FaSSIF and LQ-FaSSIF at different pH values (pH 1.7, 5.0, 6.0, 6.5, 7.0 and 7.4; see Fig. 1). The pH of each sample did not change during the experimental period. The results showed that the solubility of the glyburide was highest in the LQ-FaSSIF (43.21 μg/mL) at pH 7.4, and decreased from the high quality HQ-FaSSIF, SIF down to BL-FaSSIF. The solubility in all media decreased from a high pH to a low pH due to the drug's pK_a of 5.3. As a weak acid, glyburide has a higher solubility in a basic aqueous environment. However, it can be considered as a poorly soluble drug considering the entire physiological pH range. The results showed that glyburide had higher solubility in FaSSIF compared to BL-FaSSIF

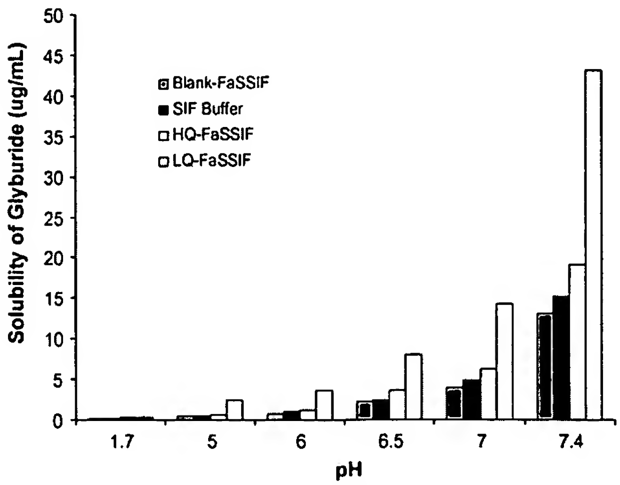

Fig. 1 – Solubility of glyburide in different media ($n = 3$).

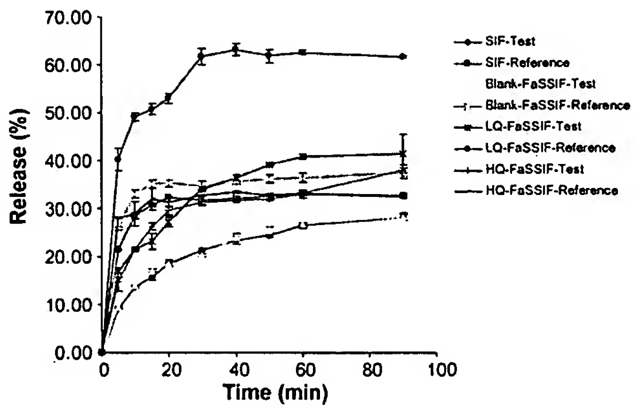

Fig. 2 – Dissolution profiles of two formulations in different dissolution media at pH 6.5.

or SIF. FaSSIF contains lecithin and bile salts (sodium taurocholate). The concentrations of bile salts and lecithin in FaSSIF are adapted to physiological conditions (Dressman et al., 1998). Bile salts and lecithin can increase the wetting process for the lipophilic drugs and solubilize the drug into the micelles formed by bile salts and lecithin. Therefore, pH and micelles impact the solubility of glyburide. This is in accordance with results reported by Jinno et al. (2000) for piroxicam. Our solubility study showed that the micelles formed by LQ bile salt and LQ lecithin were able to solubilize glyburide better compared to the chemically purer HQ bile salt and HQ lecithin. The difference between HQ- and LQ-FaSSIF is the chemical grade of the bile salt and lecithin used to prepare the media. LQ-media contain other components like glycocholic, cholic, deoxycholic and other bile acids from crude ox bile to a higher extent while the HQ-media contain 97% pure sodium taurocholate. The different composition impacts the solubility of glyburide. Woodford (1969) reported that the addition of 1-monoolein to a taurocholate micelle system increased the solubility of cholesterol. He concluded that a three-component micelle system (monoolein–taurocholate–cholesterol) form different micelles compared to the pure taurocholate cholesterol system. The improved solubility of glyburide in LQ-media might be due to similar effects caused by the presence of the other bile components. BL-FaSSIF and SIF are plain buffers. They mainly influence the solubility of glyburide by means of pH. Such media might not reflect the physiological environment of GI tract due to the lack of micelle solubilization.

3.2. *In vitro dissolution studies at pH 6.5*

The common limiting factor for oral absorption of class II drug substances is their lack of dissolution due to limited solubility (Galia et al., 1998). For such drugs solubility might be the major factor in influencing the dissolution behavior. In order to establish meaningful IVIVCs, the *in vitro* dissolution tests have to simulate the *in vivo* dissolution behaviors or need at least a relationship which can be established using a scaling factor (Löbenberg et al., 2000). Fig. 2 shows the dissolution of the reference and test formulations in four different media at pH 6.5. The drug release of the test formulation in pH 6.5 media was slower compared to the reference formulation during the first 30 min. This was observed in all four dissolution media. Both formulations had the highest release in LQ-FaSSIF. The graph shows that the drug release of the reference and test formulations in LQ-FaSSIF was over 60 and 40%, respectively, within 90 min. In the other three media, the drug releases were below 40% within 90 min which is due to limited drug solubility in these media as confirmed by results of the solubility study. Table 1 shows the values of two comparison factors: (f_1) is the difference factor and (f_2) is the similarity factor. Both can be used to assess dissolution profiles between formulations. The f_1 and f_2 factors were equal to 79.6 and 30.1, respectively, when the dissolution tests were performed in LQ-FaSSIF. A higher f_1 value corresponds to dissimilarity while an f_2 value below 50 indicates differences between two dissolution profiles (Costa and Lobo, 2001). The f_1 obtained from LQ-FaSSIF is the highest among the four media and the f_2 factors obtained from LQ-FaSSIF is the lowest compared to the other three media. This indicates that the LQ-FaSSIF differentiated formulation differences better compare to the other media. The f_2 factors of dissolution profiles in SIF and BL-FaSSIF were 47.8 and 42, respectively. The f_1 factors are 51.9 and 67.9, respectively. Although in these media the f_1 and f_2 factors showed differences in the dissolution profiles, the values of the f_2 factors were close to the critical value 50 which divides between similarity and dissimilarity (Costa and Lobo, 2001). In contrast the comparison of the formulations in HQ-FaSSIF produced an f_1 value of 10.5 and an f_2 factor of 61.2. In this medium, the dissolution profiles would be considered similar. The results above show that LQ-FaSSIF can best differentiate between the

Table 1 – f_1 and f_2 factors comparing the dissolution profiles between a reference and a test formulation at pH 6.5

	LQ-FaSSIF	HQ-FaSSIF	SIF	BL-FaSSIF
f_1	79.6	10.5	51.9	67.9
f_2	30.1	61.2	47.8	42

dissolution behaviors of both formulations. This might be due to a different interaction of the formulation components with the components of the dissolution media. Vertzoni et al. (2004) showed that the LQ-FeSSIF had a substantial impact on the dissolution profiles of two highly lipophilic drugs. The study showed that the *in vitro* dissolution in LQ-FeSSIF was more suitable in describing the *in vivo* dissolution performance of those two drug products. In an earlier study, Löbenberg et al. (2000) reported that the drug releases of two glyburide formulations in a HQ-FaSSIF were able to differentiate between the dissolution behaviors of two formulations. However, in the present study HQ-FaSSIF exhibited the lowest discriminative power between both tested formulations. The different results might be due to the different batches of lecithin and sodium taurocholate used to prepare the media and the volume used for the tests (Sznitowska et al., 2002). Leng et al. (2003) investigated the formation of vesicles and micelles using bile salts and lecithin. They identified different stages of these vesicle formations. Different vesicle shapes and mono and multi-laminar vesicles can be formed. This was shown to be highly sensitive to environmental and physicochemical factors of the used bile salts and lecithin. This effect might also explain the discriminative power of certain biorelevant media. The drug and excipients of pharmaceutical formulations might interact differently with media and either support or destruct the formation of certain vesicles and might solubilize the drug differently compared to other vesicles. However, this has to be investigated more. The characterization and investigation of the effect of vesicle structure on the dissolution behavior can help to further standardize biorelevant media.

3.3. *Dynamic dissolution studies*

The dynamic dissolution test of the two formulations was performed following the pH profile used by the ACAT model as discussed earlier. Fig. 3 shows the drug release under changing pH values in different dissolution media. The drug release of the test formulation was slower than that of the reference formulation. This was observed in all media. Compared to the single pH (Fig. 2) the drug release for both formulations was slower in all media within the first 30 min. However, after 4 h the drug release was higher in all media. This can be attributed to the solubility of glyburide at different pH values. The drug release increased when the pH increased. When the pH was changed to 7.5, the drug releases reached a plateau for both formulations in all media. When the pH of the media was changed from 7.5 to 5.0, the drug concentration in LQ-FaSSIF had no change and stayed on the plateau for 1 h. Our results show that the micelles formed keep the glyburide in solution without precipitation despite the unfavorable pH. The LQ lecithin and LQ bile salts enhanced either the stability of the micelles or the increase in drug solubilization. However, in HQ-FaSSIF, the drug concentration dropped slightly from 83 to 79 and 78 to 71%. A t-test indicated that there are no statistically significant differences between the drug release changes. However, the observed decrease might be due to a precipitation of some glyburide due to the pH change and the unfavorable pH condition. A more pronounced precipitation was observed in the SIF and BL-FaSSIF. The concentrations dropped from above 75 to under 12% for both formulations. This can be explained by the nature of SIF and BL-FaSSIF which are plain buffers.

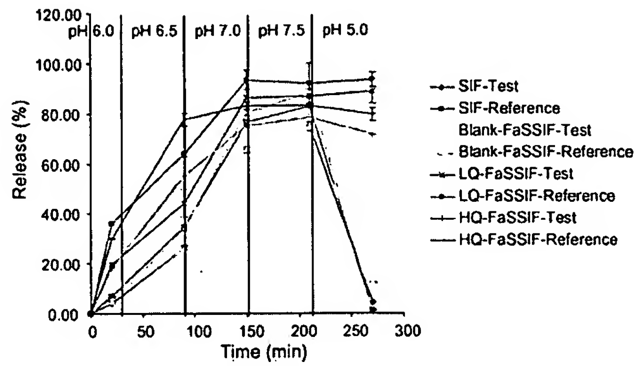

Fig. 3 – Dissolution profiles of two formulations in different dissolution media using a pH gradient.

Comparing the 90 min drug release values of the fixed pH experiment and the dynamic dissolution experiment (Table 2) reveals that the pH change had an impact on the solubilization capacity of the HQ-FaSSIF. At 90 min the pH of both experiments was the same. While the drug release in the two buffers (SIF and BL-FaSSIF) and the LQ-FaSSIF were nearly the same for each formulation and media, and a significant increase in drug release was observed in the HQ-FaSSIF. At all other pH values the HQ-FaSSIF had lower drug concentrations compared to the LQ-FaSSIF. This observation supports the earlier discussed formation of different types of vesicles and the impact of environmental factors on this process. However, such effects have to be studied in more detail.

Table 2 – Comparison of the drug releases (%) at 90 min ($n = 3$) at pH 6.5 using dynamic and single pH dissolution protocols for a reference and a test formulation

	Reference formulation		Test formulation	
	Single pH 6.5	Dynamic pH	Single pH 6.5	Dynamic pH
LQ-FaSSIF	61.73 ± 0.18	63.75 ± 0.86	41.53 ± 4.00	44.02 ± 5.48
HQ-FaSSIF[a]	32.58 ± 0.28	77.75 ± 2.53	38.01 ± 1.12	54.99 ± 0.07
SIF	27.0 ± 0.60	34.74 ± 0.65	28.30 ± 0.58	26.11 ± 1.01
BL-FaSSIF	37.45 ± 1.10	33.91 ± 0.58	28.40 ± 0.82	26.43 ± 1.02

[a] t-Tests indicated a statistically significant difference in the drug releases between the single pH and dynamic dissolution test.

3.4. *Permeability studies*

The human permeability (P_{eff}) of the glyburide was estimated by GastroPlus™ as 3.5×10^{-4} cm/s, using *in vitro* Caco-2 data. Vogelpoel et al. (2004) suggested that, if the human permeability (P_{eff}) of a drug is above 2×10^{-4} cm/s or the bioavailability is over 90%, this drug can be considered as a highly permeable drug. Literature shows that glyburide's bioavailability can be up to 100% depending on the formulation (Neugebauer et al., 1985). Therefore, glyburide can be classified as a highly permeable drug as confirmed using the Caco-2 model. Based on the BCS (Amidon et al., 1995), glyburide is a typical class II drug, which has high permeability and low aqueous solubility.

3.5. *Computer simulations*

The computer simulations using the GastroPlus™ were performed by using dissolution profiles and pH-solubility profiles as major input functions. All the physical and chemical properties of the glyburide described previously were kept the same. The human permeability (P_{eff}) of the glyburide was estimated as 3.5×10^{-4} cm/s. A parameter sensitivity analyses using GastroPlus™ showed that the predicted C_{max} and AUC will not be significantly influenced between a permeability of 2×10^{-4} and 10×10^{-4} cm/s. This confirms that glyburide is a typical class II drug and dissolution and not permeability is the limiting factor in oral absorption (Löbenberg and Amidon, 2000). Using the single pH dissolution profiles, the simulated plasma concentration profiles did not match the clinical data. The predicted C_{max} and AUC were half and one-third of observed data, respectively (Table 3). The prediction errors of the C_{max} and AUC were ±38, 63, 59 and 67% for the reference and test formulations, respectively. The *in vitro* dissolutions at fixed pH condition were not able to simulate the *in vivo* plasma levels. Therefore, the *in vivo* dissolution seems to be different.

Using the dynamic pH dissolution profiles as input function for the simulations showed that only the dissolution profiles obtained from LQ-FaSSIF were able to predict the clinically observed data (Fig. 4). The prediction errors of C_{max} and AUC were ±7, 14, 4 and 0.7% for the reference and test formulations, respectively (Table 3). The dynamic dissolution profiles obtained from LQ-FaSSIF showed the best simulation results compared to the results obtained from the other dissolution media (Table 3). The prediction errors of the AUC and C_{max} obtained from the other three media such as HQ-FaSSIF, BL-FaSSIF and SIF are much higher (up to ±28%) compared to LQ-FaSSIF. The goodness of fit (linear regression) for the simulation obtained from LQ-FaSSIF, regression coefficient for the reference and test formulations were 0.94 and 0.93, respectively. The simulation results clearly showed that an *in vitro/in vivo* relationship between the dynamic dissolution in LQ-FaSSIF and the *in vivo* plasma curves exists. The *in vitro* dissolution following the dynamic pH profiles seems to mimic the *in vivo* dissolution. The USP 28 describes in Chapter 1088 different levels of IVIVC. A level A correlation is a point to point correlation and the strongest correlation possible (USP 28). The *in vitro* dissolution properties can serve as surrogate for *in vivo* performance. Our results in the different media show that LQ-media successfully predicted the oral performance of the two formulations. Applied *in vitro* dissolutions seem to predict the *in vivo* dissolution as required for a level A correlation.

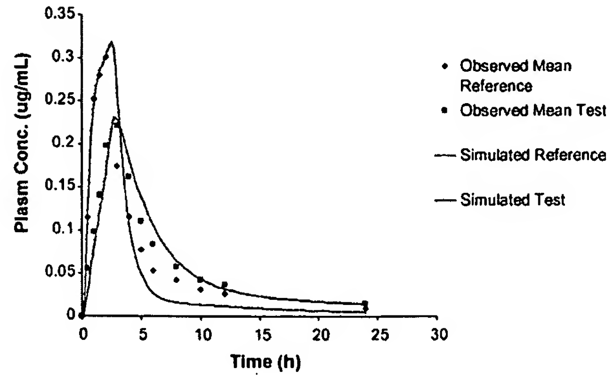

Fig. 4 – Comparison of the simulated and observed data using dynamic dissolution data as input into the simulation software.

Table 3 – Comparison of pharmacokinetic parameters of a bioequivalence study between observed and simulated data (observed reference—C_{max}: 301 ng/mL; AUC_{0-24}: 1359.6 ng/(mL h); observed test—C_{max}: 221 ng/mL; AUC_{0-24}: 1441.3 ng/(mL h))

	Simulated				Prediction error (%)			
	Reference		Test		Reference		Test	
	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC	C_{max}	AUC
(a)	187	499	92	477	38	63	59	67
(b)	385	1180	189	1230	28	13	14	15
(c)	355	1100	190	1240	18	19	14	14
(d)	384	1010	202	1270	28	26	8	12
(e)	318	1170	230	1452.1	7	14	4	0.7

(a) Single pH 6.5; (b) BL-FaSSIF; (c) SIF; (d) HQ-FaSSIF; (e) LQ-FaSSIF. C_{max}: ng/mL; AUC: ng/(mL h).

4. Conclusions

Biorelevant dissolution media are a complex mixture of bile salts and lecithin. The study showed that environmental changes which *in vivo* dynamically happen in the gastrointestinal tract have an impact on the solubilization of glyburide, as indicated by the LQ- and HQ-media. These effects have to be studied in more detail. Computer simulations using the ACAT model showed that the LQ-FaSSIF data were best able to predict plasma levels of two investigated glyburide formulations if a pH gradient was applied. The used *in vitro* and *in silico* methods were able to predict the oral performance of two glyburide formulations. An *in vitro/in vivo* correlation (IVIVC) could be established.

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A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of *in Vitro* Drug Product Dissolution and *in Vivo* Bioavailability

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A biopharmaceutics drug classification scheme for correlating *in vitro* drug product dissolution and *in vivo* bioavailability is proposed based on recognizing that drug dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extent of drug absorption. This analysis uses a transport model and human permeability results for estimating *in vivo* drug absorption to illustrate the primary importance of solubility and permeability on drug absorption. The fundamental parameters which define oral drug absorption in humans resulting from this analysis are discussed and used as a basis for this classification scheme. These **Biopharmaceutic Drug Classes** are defined as: Case 1. High solubility-high permeability drugs, Case 2. Low solubility-high permeability drugs, Case 3. High solubility-low permeability drugs, and Case 4. Low solubility-low permeability drugs. Based on this classification scheme, suggestions are made for setting standards for *in vitro* drug dissolution testing methodology which will correlate with the *in vivo* process. This methodology must be based on the physiological and physical chemical properties controlling drug absorption. This analysis points out conditions under which no *in vitro-in vivo* correlation may be expected e.g. rapidly dissolving low permeability drugs. Furthermore, it is suggested for example that for *very rapidly* dissolving high solubility drugs, e.g. 85% dissolution in less than 15 minutes, a simple one point dissolution test, is all that may be needed to insure bioavailability. For slowly dissolving drugs a dissolution profile is required with multiple time points in systems which would include low pH, physiological pH, and surfactants and the *in vitro* conditions should mimic the *in vivo* processes. This classification scheme provides a basis for establishing *in vitro-in vivo* correlations and for estimating the absorption of drugs based on the fundamental dissolution and permeability properties of physiologic importance.

KEY WORDS: bioavailability; drug absorption; mathematical modeling; *in vitro–in vivo* correlation; intestinal permeability.

INTRODUCTION

Drug dissolution is a prerequisite to drug absorption and clinical response for almost all drugs given orally. Exceptions to this general requirement such as 'GI' drugs, e.g. resins, antidiarrials, adsorbants, some laxatives, etc. are not considered in this report. While this recognition is obvious and correlations between *in vitro* dissolution and *in vivo* bioavailability for oral products are extensive, comprehensive models for predicting oral drug absorption based on drug dissolution have been limited (1-5). This is due, in part, to the complexity of the processes occurring in the gastrointestinal tract and in part to the complex pharmacokinetics of drugs making it difficult to obtain accurate adsorption estimates from systemic availability. For example, any effort to model the gastrointestinal tract requires consideration of; fasted/fed state, cyclical fasted state motility, gastric emptying and intestinal transit, variable lumen contents; e.g. pH, enzymes, surfactants and dietary lipids, as well as drug absorption mechanism, permeability, and variation in drug physicochemical properties during gastrointestinal transit (6-13). Recently we have developed a simplified macroscopic approach to drug absorption and demonstrated a good correlation between the extent of drug absorption and the intestinal membrane permeability in an animal model that is mechanism of absorption independent (2). In addition we have developed a drug dissolution and absorption model for water insoluble drugs that limits to the previous macroscopic result under appropriate conditions (3,13). These models point out very clearly that the key parameters controlling drug absorption are three dimensionless numbers; an Absorption Number, An, a Dissolution Number, Dn and a Dose Number Do; representing the fundamental processes of membrane permeation, drug dissolution and dose, respectively. In this report we use this approach to set up a theoretical basis for correlating *in vitro* drug dissolution with *in vivo* bioavailability. This analysis has considerable significance for drug bioavailability and bioequivalence standards and *in vitro dissolution methodology* since it clarifies the 'regimes' of the drug absorption process and offers a basis for determining when and under what conditions *in vitro-in vivo* correlations are to be expected. Furthermore, this analysis leads to the suggestion that drug bioavailability standards should be set on the basis of a **Biopharmaceutics Drug Classification** scheme that follows from this analysis.

Theoretical Considerations

The fundamental starting point for this analysis is;

$$J_w = P_w \cdot C_w \qquad \text{equation 1}$$

where, $J_w(x,y,z,t)$ is the drug flux (mass/area/time) through the intestinal wall at any position and time, $P_w(x,y,x,t)$ is the permeability of this (complex) membrane, and $C_w(x,y,z,t)$ the drug concentration at the membrane (intestinal) surface. This is Fick's First Law applied to a membrane and applies at each point along the membrane (14) i.e. equation 1 is a local law pertaining to each point along the intestinal membrane. It is assumed that sink conditions (drug concentration equals zero) exist for the drug inside this complex membrane and that P_w is an effective permeability. The plasma *may be* assumed to be the physiological sink since concentrations in the plasma are generally more than several orders of magnitude below that in the intestinal lumen in humans (15). The drug absorption rate, i.e. the rate of loss of drug from

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the intestinal lumen, assuming no luminal reactions, at any time is;

$$\text{Absorption Rate} = dm / dt = \int\int_A P_w C_w dA \qquad \text{equation 2}$$

where the double integral is over the entire gastrointestinal surface. The total mass, M, of drug absorbed at time t is:

$$M(t) = \int_0^t \int\int_A PwCwdAdt \qquad \text{equation 3}$$

These mass balance relations are very general since the surface can be of arbitrary shape and the concentration at the membrane wall and permeability can have any dependence on position and time. For full generality the permeability, P_w, must be considered to be *position dependent* as well as *time dependent*. The time dependence may be due to a dependence on drug concentration as in the case of carrier mediated transport, through indirect effects on the membrane of other components of the dosage form, or due to other physiological or biochemical variations such as modulation of tight junction permeability, changes in luminal contents, up or down regulation of membrane transporters or changes in membrane structure or composition. The permeability is very often position dependent from duodenum, jejunum, ileum and colon due to the different morphology and mucosal cell differentiation down the intestine e.g. amino acid and di/tripeptide transport in the jejunum and ileum, but not colon.

Based on equations 1 and 2 above the following principle for bioavailability may be stated:

If two drug products, containing the same drug, have the same concentration time profile at the intestinal membrane surface then they will have the same rate and extent of absorption.

This statement furthermore implies that;

If two drug products have the same *in vivo* dissolution profile *under all luminal conditions*, they will have the same rate and extent of drug absorption.

These general principles assume that there are no other components in the formulation that affect the membrane permeability and/or intestinal transit. If that were the case then the dissolution standard would have to include specifications for the dissolution of those components as well. This second statement follows from equations 1 and 2 since the *in vivo* dissolution rate will determine $C_w(x,y,z,t)$. Due to variable gastrointestinal transit and lumen contents at time of dosing as well as differences in special populations, i.e. differences in the gastrointestinal state of an individual, intra individual, inter individual and special population gastrointestinal variation, variation in the rate and extent of absorption are to be expected.

Two aspects of this broad principle are considered in more detail below;

i.) The relationship between *in vivo* drug dissolution and the solution or intestinal wall concentration, C_w, and

ii.) The relationship between the *in vivo* dissolution and *in vitro* dissolution.

In Vivo Dissolution and Luminal/Surface Concentration

The relationship between drug dissolution *in vivo* and the concentration of drug at the absorbing surface of equation 2 or 3 is complex due to the complex hydrodynamics and contents of the gastrointestinal tract. Various approaches to modeling these processes have been taken. These include; mixing tank and plug flow models, mixing tanks in series and dispersed plug flow models (1-5,16-19). In virtually all models the wall permeability is treated as an effective wall permeability and includes an unknown aqueous resistance[6] That is:

$$P_e = P_a P_w / (P_a + P_w) \qquad \text{Equation 4}$$

P_w is the wall permeability discussed above. P_a is the apparent permeability to mass transport to the intestinal membrane. A lower limit to this permeability can be estimated using a laminar flow hydrodynamic model for the intestinal 'fluid' (20,21). Turbulence due to intestinal wall contractions and curvature would lead to large values of P_a. For laminar flow, P_a is estimated by:

$$P_a^{-1}(x) = 1.47(D / R)Gz^{1/3} (x / L)^{1/3} \qquad \text{Equation 5}$$

in a circular tube, under sink conditions in the diffusional entrance region (21,22). Assuming a mixing length in the human intestine of 10 cm P_a is estimated to be 2×10^{-5} cm/sec. ($\approx$ 0.072 cm/hr)[7] in an aqueous fluid (i.e. viscosity of water). This represents a lower limit of P_a in this simple fluid model.

An alternate line of reasoning however, suggests that P_a is much larger than the above estimate and *not a significant resistance to mass transport for most cases of drug absorption* at least in the upper gastrointestinal tract. For two organic molecules the aqueous permeability is principally a function of their aqueous diffusivity when the media is the same (eqn 5, (22)). Since, the extent of nutrient absorption is 100 % over less than half of the small intestine, P_a must be at least this large in the upper small intestine. The measured permeability of glucose (15) in humans is about 1×10^{-3} cm/sec (3.6cm/hr). This provides an experimental estimate of the lower limit of P_a *in vivo* in the jejunum. Since the aqueous diffusion coefficient of drugs such as α-methyldopa, cimetidine, or furosemide would be similar to that for nutrients such as glucose or the amino acids and their extent of absorption is less than 100% it can be concluded that the limitation to drug absorption is not usually the aqueous mass transport coefficient, P_a. The intestinal wall permeabilities for drugs that are less than 100% absorbed must be significantly less than that for a nutrient such as glucose or an amino acid and P_a cannot be rate limiting for drugs that are in solution i.e. high solubility drugs. This implies that P_w is the determining component in P_e, i.e.

[6] The major exception to this is for laminar flow models where defined hydrodynamics are assumed. This is appropriate for more controlled intestinal perfusion systems and allows for a more direct estimate of the intestinal membrane permeability.

[7] The values used to obtain this estimate: $D = 5 \times 10^{-6}$ cm/sec, L = 200 cm, R = 1 cm, Q = 0.5 ml/min.

$$P_e \cong P_w (< 100\% \text{ absorbed drugs})$$

This indicates that the intestine can be treated as well mixed radially i.e. locally and that the intestinal membrane is the dominant resistance to drug absorption.

Based on the above analysis, one would expect to obtain a good correlation between extent of drug absorption and intestinal membrane permeability for *high solubility* drugs that are dosed in solution or for high solubility drugs in dosage forms that dissolve very rapidly. Figure 1 shows a plot of fraction absorbed in humans vs. measured human jejunal membrane permeabilities (23-26). The insert in this plot is of Log(100-F) vs. P_w which is expected to be linear for a simple plug flow model of intestinal content movement (2). From this plot, a drug with a permeability greater than 2-4 $\times 10^{-4}$ cm/sec or about 1 cm/hr would be well absorbed with the expected fraction absorbed being greater than 95%. The correlation in Figure 1 is absorption mechanism independent since it is measuring the actual mass transfer resistance to drug absorption for high solubility drugs (2,11). This permeability can be used as a fundamental parameter for establishing drug properties that will lead to 'good' absorption rates.

The maximal absorption rate occurs when the drug concentration is at its solubility, C^s, and from equation 1 and 3,

$$J^{max} = P_w C_w^s \qquad \text{equation 6}$$

and

$$M^{max}(t) = \int_0^t \iint_A P_e C_w dA dt$$

$$C_w = C_s, C \geq C_s$$

$$C_w = C, C \leq C_s \qquad \text{equation 7}$$

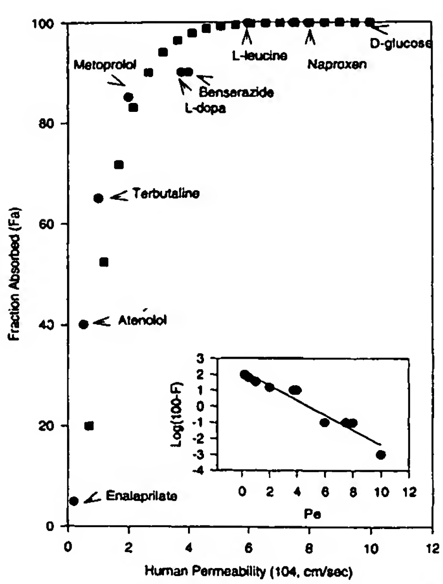

Fig. 1. Graph of the extent of absorption vs. human intestinal jejunal permeabilities.

This represents solubility limited absorption and assumes that the dissolution rate is sufficiently rapid to keep the solution concentration at saturation.

In Vitro–In Vivo Drug Dissolution and Absorption

In order to develop a more quantitative and predictive model for drug absorption rates, it is necessary to develop (microscopic) models of the flow, dissolution, absorption, and reaction processes occurring in the intestine. In general this is quite complex. However, a simple model that considers a segment of intestine over which the permeability may be considered constant, a plug flow fluid with the suspended particles moving with the fluid, no significant particle-particle interactions (i.e. aggregation) and dissolution in the small particle limit, leads to the following pair of differential equations in dimensionless form (3);

$$dr^* / dz^* = -(Dn / 3)(1 - C^*) / r^* \qquad \text{equation 8}$$

and

$$dC^* / dz^* = DoDnr^*(1 - C^*) - 2AnC^* \qquad \text{equation 9}$$

where

$$z^* = z / L = (v_z / L)t = t^*$$

$$t^* = t / (L / v_z) = t / (AL / Q) = t / (V / Q)$$

where: L = tube length, v_z = axial fluid velocity in the tube, A = tube surface area area $= 2\pi RL$, R = tube radius, Q = fluid flow rate $= Av_z$. The three important dimensionless groups are:

$$\text{Do} = \text{Dose Number} = \frac{M_o / V_o}{C_s}$$

$$\text{Dn} = \text{Dissolution Number} = \frac{DC_s}{r_o} \cdot \frac{4\pi r_o^2}{\frac{4}{3}\pi r_o^3 \rho} \cdot t_{res}$$

$$= t_{res} \cdot 3DC_s / \rho r_0^2 = t_{res} / t_{Diss}$$

$$\text{An} = \text{Absorption Number} = \frac{P_{eff}}{R} \cdot t_{res} = t_{abs}^{-1} \cdot t_{res}$$

$$t_{res} = \pi R^2 L / Q = \text{mean residence time.}$$

$$t_{Diss} = \frac{r_0^2 \rho}{3DC_s} = \text{time required for a particle of the drug to dissolve.}$$

$$t_{abs}^{-1} = k_{abs} = (S / V)P_{eff} =$$

$$2 \cdot \frac{P_{eff}}{R} = \text{the effective absorption rate constant.}$$

Where, in addition to the symbols defined previously, S is surface area, V is volume, M_o is the dose, and r_o is the initial particle radius.

This analysis while simplified, emphasizes the three fundamental parameters controlling drug dissolution and ab-

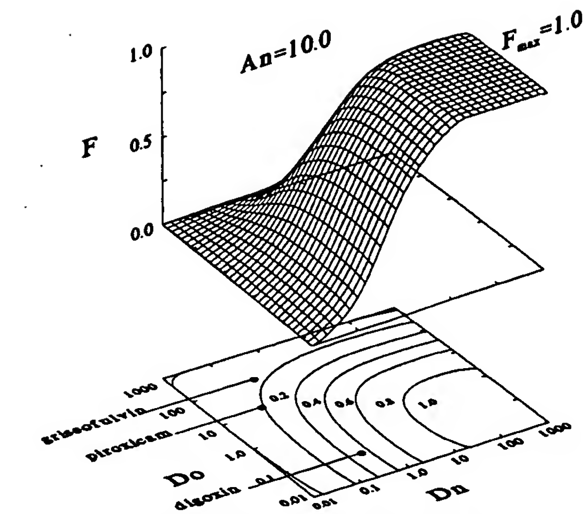

Fig. 2. Graph of estimated fraction dose absorbed vs Dissolution Number, Dn, and Dose Number, Do, for a high permeability drug. An = 10 corresponds to a drug with a permeability approximately that of glucose.

sorption. Figure 2 shows a typical profile for high permeability drug. This profile for a high permeability drug (An = 10)[8] illustrates the sharp dependence of extent of drug absorption on the Dose and Dissolution Numbers when they are in critical ranges around one for a well absorbed (high permeability) drug. It is also evident from the figure that at high dose numbers, the extent of absorption is only weakly dependent on the Dissolution Number. The limiting solution to equations 8 and 9 for this region is

$$F = 2An \,/\, Do$$

and is independent of dissolution rate (2,3). This is the *solubility limited* absorption region. Thus, in certain regions drug absorption is very dependent on drug dissolution rate and dose and in other ranges it is only weakly dependent.

[8] Values for An $\geq$ 6 represent sink conditions for drugs with low solubility, high permeability. Assuming conservative estimates for the parameters which make up An, ie, $P_{eff} = 1 \times 10^{-3}$ cm/sec, t_{res} = 180 min., and R = 1 cm, An = 10.

For estimating *in vivo* absorption, the extent of solubilization particularly in the small intestine is critical to making good estimates. Drugs with a high Dose Number must be effectively solubilized *in vivo* for good absorption. However, at the present time, a conservative estimate of the Dose Number is recommended, i.e., the *minimum* solubility of the drug should be determined in the physiological pH range (1-8) and temperature.

Table I presents some dose, solubility, Dose Number and estimated Dissolution Number data for a number of drugs. The drugs in Table I were chosen to illustrate the significance of the dose of a drug as well as its solubility. The drugs griseofulvin and digoxin are representative examples. Both compounds have similar solubilities (0.015 mg/ml and 0.024 mg/ml respectively) and it can be assumed that based on the solubility data, both drugs should be absorbed equally. However, based on the Dose Number of the two compounds (133 for griseofulvin and 0.08 for digoxin) the fraction of a dose of digoxin absorbed is expected to be much greater than that of griseofulvin (Figure 2). The absorption of digoxin is up to 100% for a solubilized form (27). While the relative bioavailability of griseofulvin can be improved by a factor of 1.7 via micronization, suggesting incomplete bioavailability (28). It is important to note that the solubility, and therefore the Dose and Dissolution Number, of a drug *in vivo* is difficult to estimate precisely due to potential aggregation and the unknown extent of solubilization, hence the actual absorption of a compound can only be estimated to be in a range depending on the assumed *in vivo* surface area and solubilization. However, this analysis allows for comparisons to be made among delivery systems and dosage forms for the same drug and estimates to be made based on assumed *in vivo* solubilization and surface area.

Permeability–Solubility Drug Classification

The above analysis suggests that correlations between drug dissolution and drug absorption are best done using the fundamental dimensionless groups, Do, Dn, and An. However, given the definition of these terms, it is clear that permeability and solubility are key underlying parameters controlling drug absorption. Thus, drugs can be divided into high/low solubility-permeability classes and the expectations regarding *in vitro-in vivo* correlations more clearly stated.

Table I. Calculated Parameters for Representative Drugs

Drug	Dose (mg)	C_S^{min} (mg/ml)[a]	V_{sol} (ml)[b]	Do[c]	Dn[d] (estimated intrinsic)
Piroxicam	20	0.007	2,857	11.4	0.15
Glyburide	20	<0.100	133	>0.80	0.78
Cimetidine	800	6.000	556	0.53	129
Chlorthiazide	500	0.786	636	2.54	17.0
Digoxin	0.5	0.024	20.8	0.08	0.52
Griseofulvin	500	0.015	33,333	133	0.32
Carbamazepine	200	0.260	769	3.08	5.61

[a] Minimum physiologic solubilities were determined in the physiological pH range (1–8) and temperature (31, 32).
[b] Volume of solvent required to completely dissolve the dose at minimum physiologic solubility.
[c] Do = Dose/V_O/C_S^{min}, initial gastric volume, V_o = 250 ml.
[d] Assumptions: r_o = 25 μm, D = 5×10^{-6} cm²/sec, ρ = 1.2 gm/cm³, $\langle t_{res} \rangle$ = 180 min. (33).

Table II. *In Vitro–in Vivo* (IVIV) Correlation Expectations for Immediate Release Products Based on Biopharmaceutics Class

Class	Solubility	Permeability	IVIV Correlation Expectation*
I	High	High	IVIV correlation if dissolution rate is slower that gastric emptying rate, otherwise limited or no correlation.
II	Low	High	IVIV correlation expected if *in vitro* dissolution rate is similar to *in vivo* dissolution rate, unless dose is very high (see discussion).
III	High	Low	Absorption (permeability) is rate determining and limited or no IVIV correlation with dissolution rate.
IV	Low	Low	Limited or no IVIV correlation expected

* A limited correlation means that the dissolution rate while not rate controlling may be similar to the absorption rate and the extent of correlation will depend on the relative rates.

These expectations are summarized in Table II and discussed in more detail below.

Case 1. High Solubility–High Permeability Drugs. This is the case where the drug is well absorbed (though its systemic availability may be low due to first pass extraction/metabolism) and the rate limiting step to drug absorption is drug dissolution or gastric emptying if dissolution is very rapid. In this case the dissolution profile must be well defined and reproducible to insure bioavailability. For immediate release dosage forms that dissolve very rapidly, the absorption rate will be controlled by the gastric emptying rate and no correlation with dissolution rate is expected. In the fasted state the gastric emptying rate is both volume and motility phase dependent with a gastric half emptying time of between 5 and 22 min., and an overall average of 12 and 22 min. for administered volumes of 50 and 200 ml respectively, Figure 3 (9). This suggests that a dissolution specification for immediate release (IR) dosage forms of perhaps 85% dissolved in less than 15 min. may insure bioequivalence[9].

Case 2. Low Solubility–High Permeability Drugs. This is the class of drugs for which the dissolution profile must be most clearly defined and reproducible. More precisely this is the case where Absorption Number, An, is high and Dissolution Number, Dn, is low. Drug dissolution *in vivo* is then the rate controlling step in drug absorption (except at very high Do) and absorption is usually slower than for Case 1. Since the intestinal luminal contents and the intestinal membrane change along the intestine, and much more of the intestine is exposed to the drug, the dissolution profile will determine the concentration profile along the intestine for a much greater time and absorption will occur over an extended period of time. Consequently, the dissolution profile must be determined for at least 4-6 time points and for at least 85% dissolution at several physiological pH's. In addition, media conditions reflective of the *in vivo* situation, such as addition of surfactants must be considered. Drugs in this class may be expected to have variable absorption due to the many formulation and *in vivo* variables that can effect the dissolution profile. Dissolution media and methods that reflect the *in vivo* controlling process are particularly important in this case if good *in vitro-in vivo* correlations are to be obtained.

[9] Stochastic simulations could be used to more precisely define these dissolution limits.

Case 3. High Solubility–Low Permeability Drugs. For this class of drugs, permeability is the rate controlling step in drug absorption. While the dissolution profile must be well defined, the simplification in dissolution specification as in Class 1 is applicable for immediate release dosage forms where drug input to the intestine is gastric emptying rate controlled. Both the rate and extent of drug absorption may be highly variable for this class of drugs, but if dissolution is fast i.e. 85% dissolved in less than 15 min., this variation will be due to the variable gastrointestinal transit, luminal contents, and membrane permeability rather than dosage form factors.

Case 4. Low Solubility–Low Permeability Drugs. This class of drugs present significant problems for effective oral delivery. The number of drugs that fall in this class will depend on the precise limits used for the permeability and solubility classification.

This classification of drugs follows naturally from the above theoretical analysis. While drug solubility and dose are readily available, and drug particle size often available, drug permeabilities are relatively less available, particularly in humans. Drug permeabilities in an animal model (rat) are more readily available and some human values are known. Recent methodological advances in the area of human intubation will undoubtedly provide more data in the future (15,23). Some of the available human permeability data were presented in Figure 1. More human data is necessary in

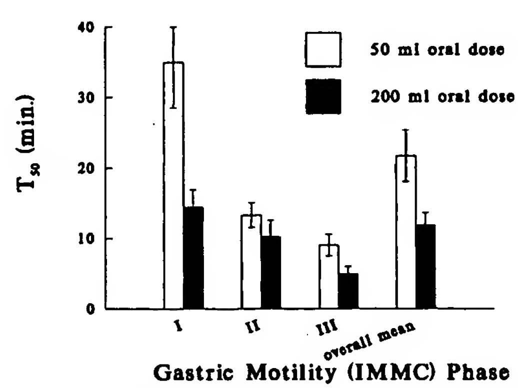

Fig. 3. Graph of measured gastric half emptying times, T50, in humans as a function of fasted state motility phase for administered volumes of 50 and 200 ml of water(9).

order to firmly establish the permeability classification criteria.

Dissolution Media and Methodology

The setting of *in vitro* standards must be done on the basis of reflecting the conditions existing *in vivo*. There is a large amount of literature on dissolution methodology and media (29). It is not the purpose of this report to suggest a methodology or media as being most appropriate. In fact the preceding analysis suggests that all that should be required is that the *in vitro* methodology/media reflect the *in vivo* situation when used to establish an IVIV correlation. There should be enough flexibility in the standards to allow for development of methods that truly reflect the *in vivo* rate controlling process for a given drug. This is particularly true for a methodology that might be used as a surrogate for an *in vivo* bioavailability test[10].

For water insoluble drugs, the relevant media for dissolution has been of considerable interest as a practical matter due to the large amount of media that may be required for a very water insoluble drug (30). The current approach that seems to be most appropriate is to use surfactants. The choice of surfactant can be important. While bile salts would be the logical choice based on physiological relevance, they are too expensive to be use on a routine basis. A surfactant such as sodium lauryl sulfate may be appropriate in many cases but the choice need not be limited to this surfactant. As noted above, the *in vivo* solubilization is a critical consideration and the dissolution media should be guided by reflecting the *in vivo* situation. If the drug is a case 2 drug (high permeability, low solubility) then absorption from solution is faster than dissolution and sink conditions are likely to prevail *in vivo*. As a general rule one should maintain sink conditions in the dissolution media if possible, such that the drug dissolves in less that 20-30% of the dissolution media.

Other factors which need to be considered, especially for case 2 drugs, are particle aggregation and the *effective* particle size *in vivo*. Quite often the first approach to increasing the dissolution rate of drugs in this class is micronization. This however, also increases the surface energy and hence potential for particle aggregation. When predicting *in vivo* bioavailability from *in vitro* dissolution profiles, it is critical that the particle size used in the model reflect the *in vivo* particle size. Therefore, it is important that the dissolution medium represent, as close as possible, the *in vivo* dissolution medium so that the apparent particle radius presented by the dosage form to the dissolution medium reflects *in vivo* conditions. Measuring the intrinsic dissolution rate, using for example rotating disk methodology, and then comparing the theoretical, measured particle(suspension), and dosage form dissolution rates can be a useful tool for determining when particle aggregation[11] is significant (22,29).

However, it must be emphasized that a strong argument for the physiological relevance of a particular surfactant containing dissolution media can not be made at this time. The dissolution media *in vivo* is a complex medium of bile salts, lecithin, cholesterol and its esters and a wide range of lipid materials that can vary considerably with meal type and diet. The physical chemistry of these systems is extremely complex. However, models for dissolution in less complex micelle systems have been developed, and it is clear that the drug solubility in the micelle phase and the effective diffusivity of the drug loaded micelle are the two most important parameters that are needed to estimate the drug dissolution rate enhancement factor (29). Further research is needed in order to establish correlations between *in vivo* representative media and the more readily available surfactant systems that could be used on a routine bases. The practical suggestion made above of using a dissolution media sufficient to dissolve the full dose of the drug in 20-30% of the media volume represents a starting point. The *in vitro* solubilization, however, should reflect the *in vivo* solubilization.

Further Consideration

Several factors will need further consideration; drugs with pH dependent solubility, drugs which exhibit complexation phenomena with gastrointestinal contents, and drugs that are unstable in the gastrointestinal tract. For drugs that exhibit pH dependent solubility, based on equations 1 and 2 governing drug absorption, it is the drug solubility at the pH of the local point in the intestine that is the most relevant pH. This pH of course varies down the intestine. The pH of the local region will influence the dissolution rate and possibility the drug permeability. This could be of importance if the dosage form altered the local pH, in which case it could alter the drug absorption rate as well as dissolution rate. In this case the dosage form dissolution specification may have to be extended to include these additional dosage form components[12].

For drugs that are unstable or interact with gastrointestinal contents in a manner so as to reduce their activity in solution e.g. complexation with ions or bile salts, dissolution rates can have a profound effect on drug absorption given the position dependence down the intestine of luminal composition. This can be the case even if the drug has high permeability (well absorbed from solution). For these drugs, where dissolution is not rapid, a multiple point dissolution profile at several pH's in addition to gastric pH should be required.

In general, the position dependence of drug absorption can be due to local pH and lumen content differences down the GI tract as well as a changing permeability. Since both of these factors can contribute to variation in rate as well as extent of absorption, it may be necessary to include in the permeability-solubility classification separate categories for drugs whose permeability, solubility, or stability varies significantly with position in the GI tract. The dissolution spec-

[10] A routine quality control dissolution methodology may be based on somewhat different considerations and it is not being suggested that this more elaborate methodology replace routine quality control methods. However, when used as a surrogate for bioavailability then the more elaborate methods may be required at least initially to establish the IVIV correlation.

[11] Particle size change can occur during processing of the dosage form, due to poor *in vivo* wetting or due to *in vivo* (re)precipitation.

[12] Drugs that may precipitate in the intestine present a particularly challenging problem due to the poorly understood and variable nucleation and crystal growth *in vivo*.

ification may need to be particularly well defined and controlled in order to insure bioequivalence for drugs with these properties.

Systemic Availability Considerations

It is clear from the above considerations that the drug absorption processes must be distinguished from the systemic bioavailability considerations. The systemic availability, F, is defined as the ratio of the dose corrected area under the plasma (blood) curves (AUC) following intravenous and oral administration;

$$F = (AUC)_{oral} * Dose_{iv} / (AUC)_{iv} * Dose_{oral}$$

and

$$F = f_a*(1-F_{TM})*(1-E_H)$$

where f_a is the fraction absorbed from the intestinal lumen. F_{TM} is the degree of metabolism by the intestinal mucosal tissue (or in the lumen) and E_H is the hepatic extraction ratio[13]. The fraction absorbed into the intestinal tissue is given by the dose normalized equation 3.

$$f_a = M(\infty) / Dose = (Dose)^{-1} \int_0^{\infty} \int\int_A P_w C_w dAdt$$

Clearly, the systemic availability will in general contain variation associated with the gastrointestinal metabolism and hepatic extraction/metabolism processes. The systemic availability will be less than that of intestinal tissue delivery, f_a, in general. For a drug with low hepatic extraction/metabolism and no GI luminal or tissue metabolism or instability, the systemic availability is equal to the fraction absorbed, f_a, from the intestinal lumen.

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日本病院薬剤師会のIF記載要領2008に準拠して作成

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アクトスOD錠は2010年7月改訂の添付文書の記載に基づき作成した。

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IF利用の手引きの概要
― 日本病院薬剤師会 ―

1. 医薬品インタビューフォーム作成の経緯

医療用医薬品の基本的な要約情報として医療用医薬品添付文書（以下、添付文書と略す）がある。

医療現場で医師・薬剤師等の医療従事者が日常業務に必要な医薬品の適正使用情報を活用する際には、添付文書に記載された情報を裏付ける更に詳細な情報が必要な場合がある。

医療現場では、当該医薬品について製薬企業の医薬情報担当者等に情報の追加請求や質疑をして情報を補完して対処してきている。この際に必要な情報を網羅的に入手するための情報リストとしてインタビューフォームが誕生した。

昭和63年に日本病院薬剤師会（以下、日病薬と略す）学術第2小委員会が「医薬品インタビューフォーム」（以下、IFと略す）の位置付け並びにIF記載様式を策定した。その後、医療従事者向け並びに患者向け医薬品情報ニーズの変化を受けて、平成10年9月に日病薬学術第3小委員会においてIF記載要領の改訂が行われた。

更に10年が経過した現在、医薬品情報の創り手である製薬企業、使い手である医療現場の薬剤師、双方にとって薬事・医療環境は大きく変化したことを受けて、平成20年9月に日病薬医薬情報委員会において新たなIF記載要領が策定された。

2. IFとは

IFは「添付文書等の情報を補完し、薬剤師等の医療従事者にとって日常業務に必要な、医薬品の品質管理のための情報、処方設計のための情報、調剤のための情報、医薬品の適正使用のための情報、薬学的な患者ケアのための情報等が集約された総合的な個別の医薬品解説書として、日病薬が記載要領を策定し、薬剤師等のために当該医薬品の製薬企業に作成及び提供を依頼している学術資料」と位置付けられる。

ただし、薬事法・製薬企業機密等に関わるもの、製薬企業の製剤努力を無効にするもの及び薬剤師自らが評価・判断・提供すべき事項等はIFの記載事項とはならない。言い換えると、製薬企業から提供されたIFは、薬剤師自らが評価・判断・臨床適応するとともに、必要な補完をするものという認識を持つことを前提としている。

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［IFの作成］

①IFは原則として製剤の投与経路別（内用剤、注射剤、外用剤）に作成される。

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［IFの発行］

①「IF記載要領2008」は、平成21年4月以降に承認された新医薬品から適用となる。

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3. IFの利用にあたって

「IF記載要領2008」においては、従来の主にMRによる紙媒体での提供に替え、PDFファイルによる電子媒体での提供を基本としている。情報を利用する薬剤師は、電子媒体から印刷して利用することが原則で、医療機関でのIT環境によっては必要に応じてMRに印刷物での提供を依頼してもよいこととした。

電子媒体のIFについては、医薬品医療機器総合機構の医薬品医療機器情報提供ホームページに掲載場所が設定されている。

製薬企業は「医薬品インタビューフォーム作成の手引き」に従って作成・提供するが、IFの原点を踏まえ、医療現場に不足している情報やIF作成時に記載し難い情報等については製薬企業のMR等へのインタビューにより薬剤師等自らが内容を充実させ、IFの利用性を高める必要がある。

また、随時改訂される使用上の注意等に関する事項に関しては、IFが改訂されるまでの間は、当該医薬品の製薬企業が提供する添付文書やお知らせ文書等、あるいは医薬品医療機器情報配信サービス等により薬剤師等自らが整備するとともに、IFの使用にあたっては、最新の添付文書を医薬品医療機器情報提供ホームページで確認する。

なお、適正使用や安全性の確保の点から記載されている「臨床成績」や「主な外国での発売状況」に関する項目等は承認事項に関わることがあり、その取扱いには十分留意すべきである。

4. 利用に際しての留意点

IFを薬剤師等の日常業務において欠かすことができない医薬品情報源として活用して頂きたい。しかし、薬事法や医療用医薬品プロモーションコード等による規制により、製薬企業が医薬品情報として提供できる範囲には自ずと限界がある。IFは日病薬の記載要領を受けて、当該医薬品の製薬企業が作成・提供するものであることから、記載・表現には制約を受けざるを得ないことを認識しておかなければならない。

また製薬企業は、IFがあくまでも添付文書を補完する情報資材であり、今後インターネットでの公開等も踏まえ、薬事法上の広告規制に抵触しないよう留意し作成されていることを理解して情報を活用する必要がある。

（2008年9月）

目　　次

Ⅴ：治療に関する項目

Ⅵ：薬効薬理に関する項目

Ⅷ：安全性（使用上の注意等）に関する項目

Ⅸ：非臨床試験に関する項目

X：管理的事項に関する項目

XI：文　　献

XII：参考資料

Ⅰ：概要に関する項目

1. 開発の経緯

当社研究所において1970年代初頭より血中脂質低下薬の探索を進めてきた中で、インスリン受容体以降のインスリンシグナル伝達経路を正常化し、インスリン抵抗性を軽減する世界で最初の化合物（シグリタゾン）を見出した。

更に強い作用を有する化合物の探索を続け、一連の化合物の中で最も優れた作用を有するピオグリタゾンを1982年に合成した。

1987年以降塩酸塩（ピオグリタゾン塩酸塩）として開発を進め、1991年4月より臨床試験を開始し、二重盲検比較対照試験を含む臨床試験において、食事療法、運動療法のみあるいは食事療法、運動療法に加えてスルホニルウレア剤使用で効果不十分な2型糖尿病*に対する有用性が確認され、1999年9月に承認された。

・食事療法、運動療法に加えてα-グルコシダーゼ阻害剤使用で効果不十分な2型糖尿病*に対して効能・効果が追加された（2002年6月）。

・食事療法、運動療法に加えてビグアナイド系薬剤使用で効果不十分な2型糖尿病*に対して効能・効果が追加された（2008年12月）。

・食事療法、運動療法に加えてインスリン製剤使用で効果不十分な2型糖尿病*に対して効能・効果が追加された（2009年3月）。

更に、水なしでも服用可能なOD錠が承認された（2010年1月）。

*インスリン抵抗性が推定される場合に限る。

2. 製品の治療学的・製剤学的特性

(1) 1日1回の投与で優れた血糖改善効果を示すインスリン抵抗性改善剤である。

(2) 膵臓からのインスリン分泌を増加させることなく、血糖降下作用を示す。

(3) 1年以上にわたって安定した血糖コントロールが得られる※。

(4) 水なしでも服用可能なアクトスOD錠もある。

(5) 承認時までのわが国での臨床試験では1日1回ピオグリタゾンとして15mg、30mg又は45mgが投与された1,368例中の364例（26.6％）に臨床検査値の異常を含む副作用が認められている。

そのうち、浮腫は女性やインスリン併用時において多くみられており［本剤単独投与及びインスリンを除く他の糖尿病用薬との併用投与：男性3.9％（26/665例）、女性11.2％（72/643例）、インスリン併用投与：男性13.6％（3/22例）、女性28.9％（11/38例）］、また、糖尿病性合併症発症例での浮腫の発現頻度は非発症例に比べ高い傾向にある［糖尿病性網膜症合併例で10.4％（44/422例）、糖尿病性神経障害合併例で11.4％（39/342例）、糖尿病性腎症合併例で10.6％（30/282例）］。また、低血糖症状はインスリン併用時に多くみられている［本剤単独投与及びインスリンを除く他の糖尿病用薬との併用投与：0.7％（9/1,308例）、インスリン併用投与：33.3％（20/60例）］。

市販後の使用成績調査（再審査終了時点）では、3,421例中の556例（16.3％）に臨床検査値の異常を含む副作用が認められている。

なお、重大な副作用として心不全の増悪あるいは発症、浮腫、肝機能障害、黄疸、低血糖症状、横紋筋融解症、胃潰瘍の再燃が上記の調査あるいは自発報告等で認められている。

※本剤投与中は、常に投与継続の可否、投与量、薬剤の選択等に注意すること。

Ⅱ：名称に関する項目

1. 販 売 名

1－1 和 名

アクトス® 錠 15

アクトス® 錠 30

アクトス® OD錠 15

アクトス® OD錠 30

1－2 洋 名

ACTOS® *Tablets* 15

ACTOS® *Tablets* 30

ACTOS® OD *Tablets* 15

ACTOS® OD *Tablets* 30

1－3 名称の由来

アクトス（ACTOS）はインスリン感受性（Insulin Sensitivity）に作用（Act On）する薬剤

Act On Insulin Sensitivity

2. 一 般 名

2－1 和 名（命名法）

ピオグリタゾン塩酸塩（JAN）

2－2 洋 名（命名法）

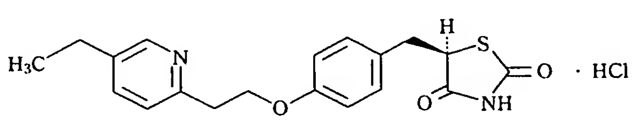
Pioglitazone Hydrochloride（JAN）

Pioglitazone（INN）

2－3 ス テ ム

-glitazone

3. 構造式又は示性式



及び鏡像異性体

4. 分子量及び分子式

分子式：$C_{19}H_{20}N_2O_3S \cdot HCl$

分子量：392.90

5. 化 学 名（命名法）

(5*RS*)-5-{4-[2-(5-Ethylpyridin-2-yl)ethoxy] benzyl} thiazolidine-2, 4-dione monohydrochloride

6. 慣用名、別名、略号、記号番号

治験番号：AD-4833

別　　名：塩酸ピオグリタゾン

7. CAS登録番号

112529-15-4

111025-46-8（Pioglitazone）

Ⅲ：有効成分に関する項目

1. 物理化学的性質

1－1 外観・性状

本品は白色の結晶又は結晶性の粉末である。

(第十五改正日本薬局方第二追補解説書 2009，C-322 廣川書店)

1－2 溶解性

本品は *N, N*-ジメチルホルムアミド又はメタノールにやや溶けやすく、エタノール（99.5）に溶けにくく、水にほとんど溶けない。

本品は0.1mol/L塩酸試液に溶ける。

(第十五改正日本薬局方第二追補解説書 2009，C-322 廣川書店)

■各種溶媒に対する溶解性（20℃）

溶媒名	本品1gを溶かすのに要する溶媒量(mL)	溶解性の表現
N,N-ジメチルホルムアミド	11	やや溶けやすい
メタノール	11～13	やや溶けやすい
エタノール（99.5）	165～175	溶けにくい
クロロホルム	289～301	溶けにくい
アセトニトリル	908～1150	極めて溶けにくい
水	＞10000	ほとんど溶けない

日局・通則による

■各種pH溶液に対する溶解度（20℃）

pH *	溶解度（mg/mL）	溶解後のpH
1.1	6.7	1.0
2.0	0.42	1.9
3.3	0.014	3.2
5.0	0.00026	4.9
7.0	0.000093	6.9
9.1	0.010	9.0
11.1	0.13	10.2
13.0	17	11.2

＊pH 1.1：0.1mol/L HCl、pH2.0～11.1：Britton-Robinson緩衝液、
pH13.0：0.1mol/L NaOH

(武田薬品・研究所)

1－3 吸湿性

本品は、25℃・31％RH、75％RH及び93％RHの条件下に14日間保存したが、重量変化は示さず、吸湿性は認められなかった。

(武田薬品・研究所)

1－4 融点（分解点）、沸点、凝固点

融点：193℃（分解点）

(武田薬品・研究所)

1－5　酸塩基解離定数

pKa_1：5.8（ピリジル基）

pKa_2：6.4（チアゾリジル基）

（武田薬品・研究所）

1－6　分配係数

本品はpH5.0～7.0では有機層に分配され、これより酸性及びアルカリ性領域ではpHの上昇又は低下とともに水層に分配されやすくなる傾向を示した。

■分配係数（20℃）

pH＊	分配係数（オクタノール/水）
1.0	0.4
3.0	85
5.0	＞1000
6.0	＞1000
7.0	＞1000
8.0	342
9.0	46
9.9	11

＊pH1.0：0.1mol/L　HCl、pH3.0～9.9：Britton-Robinson緩衝液

（武田薬品・研究所）

1－7　その他の主な示性値

◇旋光度

本品の*N, N*-ジメチルホルムアミド溶液（1→20）は旋光性を示さない。

（第十五改正日本薬局方第二追補解説書　2009，C-322　廣川書店）

2. 有効成分の各種条件下における安定性

◇各種条件下における安定性

<table>
<tr><th colspan="2">試験</th><th>温度</th><th>湿度</th><th>光</th><th>保存形態</th><th>保存期間</th><th>測定結果</th></tr>
<tr><td colspan="2">長期保存試験</td><td>25℃</td><td>60％RH</td><td>暗所</td><td>ポリエチレン袋（密閉）</td><td>36カ月</td><td>変化なし</td></tr>
<tr><td rowspan="7">苛酷試験</td><td rowspan="3">温度</td><td>40℃</td><td rowspan="3">—</td><td rowspan="3">暗所</td><td rowspan="3">無色ガラス瓶（密栓）</td><td>6カ月</td><td>変化なし</td></tr>
<tr><td>50℃</td><td>3カ月</td><td>変化なし</td></tr>
<tr><td>60℃</td><td>3カ月</td><td>変化なし</td></tr>
<tr><td rowspan="2">湿度</td><td rowspan="2">25℃</td><td>75％RH</td><td rowspan="2">暗所</td><td rowspan="2">無色ガラス瓶（開栓）</td><td rowspan="2">6カ月</td><td>変化なし</td></tr>
<tr><td>93％RH</td><td>変化なし</td></tr>
<tr><td rowspan="2">光</td><td rowspan="2">25℃</td><td rowspan="2">—</td><td>白色蛍光灯(1000lx)</td><td rowspan="2">シャーレ(ポリ塩化ビニリデン製フィルムで覆った)</td><td>60日間</td><td>変化なし</td></tr>
<tr><td>キセノンランプ(7万lx)</td><td>21時間</td><td>変化なし</td></tr>
</table>

（武田薬品・研究所）

3. 有効成分の確認試験法

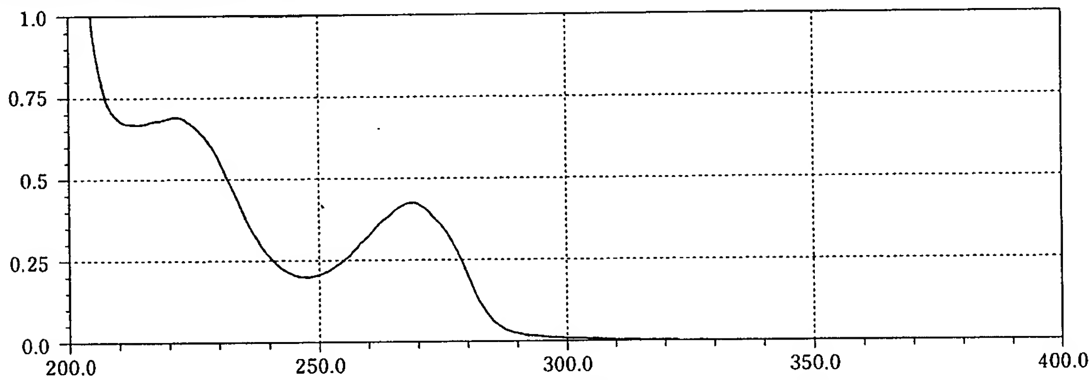
(1) 本品の0.1mol/L塩酸試液溶液（1→50000）につき、紫外可視吸光度測定法により吸収スペクトルを測定し、本品のスペクトルと本品の参照スペクトル又はピオグリタゾン塩酸塩標準品について同様に操作して得られたスペクトルを比較するとき、両者のスペクトルは同一波長のところに同様の強度の吸収を認める。

(2) 本品につき、赤外吸収スペクトル測定法の臭化カリウム錠剤法により試験を行い、本品のスペクトルと本品の参照スペクトル又はピオグリタゾン塩酸塩標準品のスペクトルを比較するとき、同一波数のところに同様の強度の吸収を認める。

(3) 本品50mgを硝酸1mLに溶かした後、希硝酸4mLを加えた液は、塩化物の定性反応（2）を呈する。

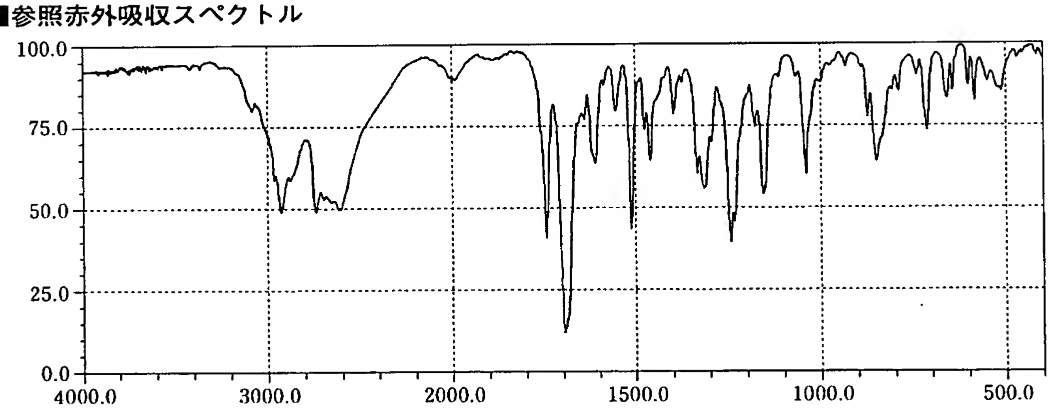
（第十五改正日本薬局方第二追補解説書　2009，C-322　廣川書店）

■参照紫外可視吸収スペクトル



（第十五改正日本薬局方第二追補解説書　2009，E-12　廣川書店）

■参照赤外吸収スペクトル



（第十五改正日本薬局方第二追補解説書　2009，E-35　廣川書店）

4. 有効成分の定量法

本品及びピオグリタゾン塩酸塩標準品（別途本品と同様の方法で水分を測定しておく）約50mgずつを精密に量り、それぞれに内標準溶液10mLずつを正確に加えて溶かした後、メタノールを加えて100mLとする。これらの液2mLずつをとり、それぞれに移動相を加えて20mLとし、試料溶液及び標準溶液とする。試料溶液及び標準溶液20μLにつき、次の条件で液体クロマトグラフィーにより試験を行い、内標準物質のピーク面積に対するピオグリタゾンのピーク面積の比Q_T及びQ_Sを求める。

ピオグリタゾン塩酸塩（$C_{19}H_{20}N_2O_3S \cdot HCl$）の量（mg）$= W_S \times \dfrac{Q_T}{Q_S}$

W_S：脱水物に換算したピオグリタゾン塩酸塩標準品の秤取量（mg）

内標準溶液：ベンゾフェノンのメタノール溶液（1→750）

試験条件

検　出　器：紫外吸光光度計（測定波長：269nm）

カ　ラ　ム：内径4.6mm、長さ15cmのステンレス管に5μmの液体クロマトグラフィー用オクタデシルシリル化シリカゲルを充てんする。

カラム温度：25℃付近の一定温度

移　動　相：酢酸アンモニウム溶液（77→10000）/アセトニトリル/酢酸（100）混液（25：25：1）

流　　　量：ピオグリタゾンの保持時間が約7分になるように調整する。

システム適合性

システムの性能：標準溶液20μLにつき、上記の条件で操作するとき、ピオグリタゾン、内標準物質の順に溶出し、その分離度は10以上である。

システムの再現性：標準溶液20μLにつき、上記の条件で試験を6回繰り返すとき、内標準物質のピーク面積に対するピオグリタゾンのピーク面積の比の相対標準偏差は1.0％以下である。

（第十五改正日本薬局方第二追補解説書　2009，C-322　廣川書店）

Ⅳ：製剤に関する項目

1. 剤　形

1－1　剤形の区別、規格及び性状

◇剤形の区別

アクトス錠：割線入りの素錠

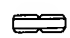
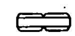
アクトスOD錠：割線入りの素錠（口腔内崩壊錠）

◇規　格

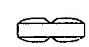
本品は定量するとき、表示量の95.0～105.0％に対応するピオグリタゾン塩酸塩（$C_{19}H_{20}N_2O_3S$・HCl：392.90）を含む。

◇性　状

■アクトス錠

	アクトス錠15			アクトス錠30		
剤　形	割線入りの素錠					
錠剤の色	白色～帯黄白色					
形　状	上 面 	下 面 	側 面 	上 面 	下 面 	側 面 
直径（mm）	7.0			7.0		
厚さ（mm）	2.4			2.5		
質量（mg）	120			120		

■アクトスOD錠

	アクトスOD錠15			アクトスOD錠30		
剤　形	割線入りの素錠（口腔内崩壊錠）					
錠剤の色	帯黄白色					
形　状	上 面 	下 面 	側 面 	上 面 	下 面 	側 面 
直径（mm）	7.1			9.1		
厚さ（mm）	2.8			3.6		
質量（mg）	120			240		

1−2　製剤の物性

1−3　識別コード

◇アクトス錠15：⊗390

◇アクトス錠30：⊗391

◇アクトスOD錠15：⊗376

◇アクトスOD錠30：⊗377

1−4　pH、浸透圧比、粘度、比重、無菌の旨及び安定なpH域

該当資料なし

2. 製剤の組成

2−1　有効成分（活性成分）の含量

◇アクトス錠15及び30：1錠中ピオグリタゾンとして15mg及び30mg含有

◇アクトスOD錠15及び30：1錠中ピオグリタゾンとして15mg及び30mg含有

2−2　添 加 物

◇アクトス錠

カルメロースカルシウム、ヒドロキシプロピルセルロース、ステアリン酸マグネシウム、乳糖水和物

◇アクトスOD錠

結晶セルロース、乳糖水和物、カルメロースカルシウム、ヒドロキシプロピルセルロース、アスパルテーム、塩化ナトリウム、黄色三二酸化鉄、クロスポビドン、ステアリン酸マグネシウム、D-マンニトール

2−3　そ の 他

該当しない

3. 懸濁剤、乳剤の分散性に対する注意

該当しない

4. 製剤の各種条件下における安定性

◇アクトス錠

(1) 長期保存試験（保存条件：25℃·60％RH、暗所、3ロット平均）

○錠15（保存形態：ガラス容器＋紙箱）

測定項目	イニシャル	12カ月	24カ月	36カ月
外　観	白色の素錠	変化なし	変化なし	変化なし
溶出率（%）	103.1	101.1	101.2	101.4
残存率（%）	100	99.7	100.2	99.3

○錠30（保存形態：ガラス容器＋紙箱）

測定項目	イニシャル	12カ月	24カ月	36カ月
外　観	白色の割線入りの素錠	変化なし	変化なし	変化なし
溶出率（%）	103.3	103.1	101.6	101.8
残存率（%）	100	100.5	100.4	99.9

○錠15（保存形態：PTP＋内袋＋紙箱）

測定項目	イニシャル	12カ月	24カ月	36カ月
外　観	白色の素錠	変化なし	変化なし	変化なし
溶出率（%）	103.1	99.5	100.7	102.3
残存率（%）	100	101.3	101.5	100.3

○錠30（保存形態：PTP＋内袋＋紙箱）

測定項目	イニシャル	12カ月	24カ月	36カ月
外　観	白色の割線入りの素錠	変化なし	変化なし	変化なし
溶出率（%）	103.3	101.6	102.1	102.1
残存率（%）	100	99.9	100.5	100.1

(2) 温度安定性（保存条件：暗所、保存形態：無色ガラス瓶（密栓））

○錠15

測定項目	イニシャル	40℃	50℃	60℃
		6カ月	3カ月	3カ月
外　観	白色の素錠	変化なし	変化なし	微帯黄白色の素錠
溶出率（%）	102.5	102.7	101.5	100.6
残存率（%）	100	100.6	100.0	100.5

○錠30

測定項目	イニシャル	40℃	50℃	60℃
		6カ月	3カ月	3カ月
外　観	白色の割線入りの素性	変化なし	ほとんど白色の割線入りの素錠	微帯黄白色の割線入りの素錠
溶出率（%）	102.8	102.3	104.6	103.3
残存率（%）	100	100.2	100.3	99.4

（武田薬品・研究所）

(3) 湿度安定性（保存条件：暗所、保存形態：無色ガラス瓶（開栓））

○錠15

測定項目	イニシャル	25℃・31％RH	25℃・93％RH
		6カ月	6カ月
外　観	白色の素錠	変化なし	帯黄白色の素錠
溶出率（%）	102.5	99.2	98.4
残存率（%）	100	100.4	101.3
硬 度（kgf）	5.7	7.2	0.8

○錠30

測定項目	イニシャル	25℃・31％RH	25℃・93％RH
		6カ月	6カ月
外　観	白色の割線入りの素錠	変化なし	帯黄白色の割線入りの素錠
溶出率（%）	102.8	99.7	96.7
残存率（%）	100	99.9	99.4
硬 度（kgf）	8.2	7.1	0.9

(4) 光安定性（保存条件：25℃、保存形態：シャーレ（ポリ塩化ビニリデン製のフィルムで覆った））

○錠15

測定項目	イニシャル	1000lx	70000lx
		60日	21時間
外　観	白色の素錠	変化なし	変化なし
溶出率（%）	102.5	101.0	101.3
残存率（%）	100	101.5	100.7

○錠30

測定項目	イニシャル	1000lx	60000lx
		60日	25時間
外　観	白色の割線入りの素錠	変化なし	変化なし
溶出率（%）	102.8	105.2	100.6
残存率（%）	100	100.1	100.7

（武田薬品・研究所）

◇アクトスOD錠

(1) 加速試験（保存条件：40℃・75％RH、暗所、3ロット平均）

○OD錠15（保存形態：ポリ瓶＋乾燥剤＋紙箱）

測定項目	イニシャル	1カ月	3カ月	6カ月
外　観	帯黄白色の割線入りの素錠	変化なし	変化なし	変化なし
溶出率（%）	98.9	99.3	99.4	99.2
残存率（%）	100	100.4	100.6	100.3

○OD錠30（保存形態：ポリ瓶＋乾燥剤＋紙箱）

測定項目	イニシャル	1カ月	3カ月	6カ月
外　観	帯黄白色の割線入りの素錠	変化なし	変化なし	変化なし
溶出率（%）	100.2	99.6	99.4	99.2
残存率（%）	100	100.3	101.3	101.0

○OD錠15（保存形態：PTP＋内袋＋乾燥剤＋紙箱）

測定項目	イニシャル	1カ月	3カ月	6カ月
外　観	帯黄白色の割線入りの素錠	変化なし	変化なし	変化なし
溶出率（%）	98.9	99.0	97.8	99.2
残存率（%）	100	99.5	100.2	99.4

○OD錠30（保存形態：PTP＋内袋＋乾燥剤＋紙箱）

測定項目	イニシャル	1カ月	3カ月	6カ月
外　観	帯黄白色の割線入りの素錠	変化なし	変化なし	変化なし
溶出率（%）	100.2	100.4	99.4	99.3
残存率（%）	100	100.1	101.1	100.0

(2) 温度安定性（保存条件：暗所、保存形態：ガラス瓶（密栓））

○OD錠15

測定項目	イニシャル	50℃	60℃
		3カ月	2カ月
外　観	帯黄白色の割線入りの素錠	変化なし	微黄赤色の割線入りの素錠
溶出率（%）	99.6	98.5	93.9
残存率（%）	100	99.6	100.1

○OD錠30

測定項目	イニシャル	50℃	60℃
		3カ月	2カ月
外　観	帯黄白色の割線入りの素錠	変化なし	微黄赤色の割線入りの素錠
溶出率（%）	98.8	97.8	90.3
残存率（%）	100	100.2	101.8

（武田薬品・研究所）

(3) 湿度安定性（保存条件：暗所、保存形態：ガラス瓶（開栓））

○OD錠15

測定項目	イニシャル	25℃・31%RH	25℃・75%RH
		3カ月	1カ月
外　観	帯黄白色の割線入りの素錠	変化なし	変化なし
溶出率(%)	99.6	100.0	99.7
残存率(%)	100	98.8	99.6
硬　度 (N)	29	28	＜10

○OD錠30

測定項目	イニシャル	25℃・31%RH	25℃・75%RH
		3カ月	1カ月
外　観	帯黄白色の割線入りの素錠	変化なし	変化なし
溶出率(%)	98.8	98.6	98.0
残存率(%)	100	100.4	100.3
硬　度 (N)	36	34	＜10

(4) 光安定性（保存条件：D65光源、保存形態：シャーレ（ポリ塩化ビニリデン製フィルムで覆う））

○OD錠15

測定項目	イニシャル	120万lx・h
外　観	帯黄白色の割線入りの素錠	変化なし
溶出率(%)	99.6	100.4
残存率(%)	100	100.5

○OD錠30

測定項目	イニシャル	120万lx・h
外　観	帯黄白色の割線入りの素錠	変化なし
溶出率(%)	98.8	99.3
残存率(%)	100	100.6

（武田薬品・研究所）

5. 調製法及び溶解後の安定性

該当しない

6. 他剤との配合変化（物理化学的変化）

該当資料なし

7. 溶 出 性

日局・溶出試験法のパドル法により試験を行う。

試験液：pH2.0の塩酸・塩化カリウム緩衝液、900mL

回転数：50回転/分

規　格：45分間の溶出率が80％以上のとき適合

（武田薬品・研究所）

8. 生物学的試験法

該当しない

9. 製剤中の有効成分の確認試験法

◇アクトス錠

本品を粉末とし、表示量に従いピオグリタゾン塩酸塩2.8mgに対応する量（粉末として錠15は約0.02g、錠30は約0.01g）をとり、0.1mol/L塩酸試液100mLを加えて振り混ぜた後、孔径0.45μmのメンブランフィルターでろ過する。ろ液につき、紫外可視吸光度測定法により吸収スペクトルを測定するとき、波長267～271nmに吸収の極大を示す。

◇アクトスOD錠

本品を粉末とし、表示量に従いピオグリタゾン塩酸塩約2.8mgに対応する量（約20mg）をとり、0.1mol/L塩酸試液100mLを加え、よく振り混ぜて均一な懸濁液とした後、孔径0.45μm以下のメンブランフィルターでろ過し、初めのろ液5mLを除いた次のろ液を試料溶液とする。試料溶液につき、紫外可視吸光度測定法により吸収スペクトルを測定するとき、波長267～271nmに吸収の極大を示す。

（武田薬品・研究所）

10. 製剤中の有効成分の定量法

◇アクトス錠

本品20個をとり、その質量を精密に量り、粉末とする。ピオグリタゾン塩酸塩（$C_{19}H_{20}N_2O_3S \cdot HCl$）約0.025gに対応する量（粉末として錠15は約0.18g、錠30は約0.09g）を精密に量り、メタノール45mLを加え、更に内標準溶液5mLを正確に加え、約2分間超音波照射して粒子を小さく分散させた後、遠心分離する。上澄液2mLをとり、移動相を加えて20mLとし、試料溶液とする。別にピオグリタゾン塩酸塩標準品約0.025gを精密に量り、メタノール45mLに溶かした後、内標準溶液5mLを正確に加える。この液2mLを量り、移動相を加えて20mLとし、標準溶液とする。試料溶液及び標準溶液20μLにつき、次の条件で液体クロマトグラフィーにより試験を行い、内標準物質のピーク面積に対するピオグリタゾンのピーク面積の比Q_T及びQ_Sを求める。

ピオグリタゾン塩酸塩（$C_{19}H_{20}N_2O_3S \cdot HCl$）の表示量に対する含量（%）

$$= W_S \times C_S \times \frac{Q_T}{Q_S} \times \frac{W}{W_T} \times \frac{1}{H} \times \frac{1}{20}$$

W ：錠剤20個の重量（mg）

W_T：錠剤の粉砕品の秤取量（mg）

W_S：ピオグリタゾン塩酸塩標準品の秤取量（mg）

C_S ：ピオグリタゾン塩酸塩標準品の含量（%）

H ：1錠中のピオグリタゾン塩酸塩の表示量（錠15は16.53、錠30は33.06）

内標準溶液 ：ベンゾフェノンのメタノール溶液（1→750）

試験条件

検　出　器：紫外吸光光度計（測定波長：269nm）

カ　ラ　ム：内径4.6mm、長さ15cmのステンレス管に5μmの液体クロマトグラフィー用オクタデシルシリル化シリカゲルを充てんしたもの

カラム温度：25℃付近の一定温度

移　動　相：アセトニトリル／0.1mol/L酢酸アンモニウム溶液／酢酸（100）混液（25：25：1）

流　　　量：ピオグリタゾンの保持時間が約7分となるように調整する。

システム適合性

システムの性能：標準溶液20μLにつき、上記の条件で操作するとき、ピオグリタゾン、ベンゾフェノンの順に溶出し、その分離度が10以上である。

システムの再現性：標準溶液20μLにつき、上記の条件で試験を6回繰り返すとき、内標準物質のピーク面積に対するピオグリタゾンのピーク面積の比の相対標準偏差は1.0%以下である。

試薬・試液

ベンゾフェノン　$C_6H_5COC_6H_5$

JIS（K8861）の特級品を用いる。ただし、本品は液体クロマトグラフィー用内標準物質として用いるとき、測定の妨害となるピークを示さない。

0.1mol/L酢酸アンモニウム溶液

酢酸アンモニウム7.7gを水に溶かし、1000mLとする。

◇アクトスOD錠

本品10個をメスフラスコにとり、0.1mol/L塩酸試液50mLを加えて崩壊させ、メタノール150mLを加えて超音波を照射して粒子を小さく分散させた後、メタノールを加えて正確に250mLとし、よく振り混ぜて均一な懸濁液とした後、孔径0.45μm以下のメンブランフィルターでろ過する。初めのろ液5mLを除き、次のろ液5mLを正確に量り、内標準溶液5mLを正確に加えた後、移動相を加えて50mLとし、試料溶液とする。別にピオグリタゾン塩酸塩標準物質約33mg（W_S mg）を精密に量り、メタノールに溶かし、正確に50mLとする。この液5mLを正確に量り、内標準溶液5mLを正確に加え、更に移動相を加えて50mLとし、標準溶液とする。試料溶液及び標準溶液20μLにつき、次の条件で液体クロマトグラフィーにより試験を行い、内標準物質のピーク面積に対するピオグリタゾンのピーク面積の比Q_T及びQ_Sを求め次式により含量を算出する。

ピオグリタゾン塩酸塩（$C_{19}H_{20}N_2O_3S \cdot HCl$）の表示量に対する含量（%）

$$= \frac{Q_T}{Q_S} \times W_S \times C_S \times D \times \frac{1}{L} \times \frac{1}{50}$$

C_S：ピオグリタゾン塩酸塩標準品の含量（%）

D ：希釈係数（OD錠15は25、OD錠30は50）

L ：ピオグリタゾン塩酸塩の表示量（OD錠15は16.53、OD錠30は33.06）

内標準溶液：ベンゾフェノンのメタノール溶液（1→5000）

試験条件、システム適合性、試薬・試液はアクトス錠の項参照

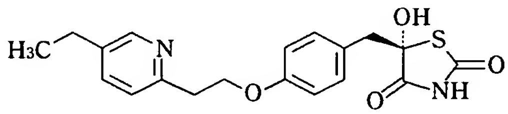
（武田薬品・研究所）

11. 力　　価

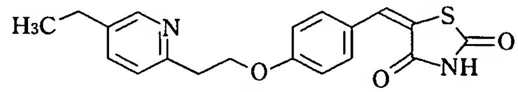
該当しない

12. 混入する可能性のある夾雑物

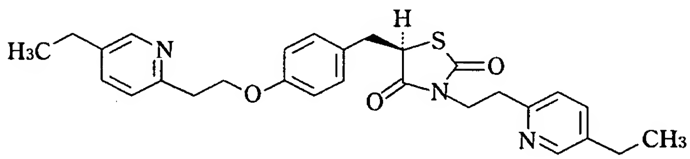
混在する主たる類縁物質には、次の［1］～［3］がある。



〔1〕



〔2〕



〔3〕

（第十五改正日本薬局方第二追補解説書　2009．C-322　廣川書店）

13. 治療上注意が必要な容器に関する情報

該当しない

14. そ の 他

該当しない

V：治療に関する項目

1. 効能又は効果

1－1 効能・効果

2型糖尿病

ただし、下記のいずれかの治療で十分な効果が得られずインスリン抵抗性が推定される場合に限る。

1. ①食事療法、運動療法のみ
   ②食事療法、運動療法に加えてスルホニルウレア剤を使用
   ③食事療法、運動療法に加えてα-グルコシダーゼ阻害剤を使用
   ④食事療法、運動療法に加えてビグアナイド系薬剤を使用
2. 食事療法、運動療法に加えてインスリン製剤を使用

1－2 効能・効果に関連する使用上の注意

糖尿病の診断が確立した患者に対してのみ適用を考慮すること。
糖尿病以外にも耐糖能異常・尿糖陽性等、糖尿病類似の症状（腎性糖尿、老人性糖代謝異常、甲状腺機能異常等）を有する疾患があることに留意すること。

2. 用法及び用量

2－1 用法・用量

1. 食事療法、運動療法のみの場合及び食事療法、運動療法に加えてスルホニルウレア剤又はα-グルコシダーゼ阻害剤若しくはビグアナイド系薬剤を使用する場合

通常、成人にはピオグリタゾンとして15～30mgを1日1回朝食前又は朝食後に経口投与する。なお、性別、年齢、症状により適宜増減するが、45mgを上限とする。

2. 食事療法、運動療法に加えてインスリン製剤を使用する場合

通常、成人にはピオグリタゾンとして15mgを1日1回朝食前又は朝食後に経口投与する。なお、性別、年齢、症状により適宜増減するが、30mgを上限とする。

2－2 用法・用量に関連する使用上の注意

全製剤共通

(1) 浮腫が比較的女性に多く報告されているので、**女性に投与する場合は、浮腫の発現に留意し、1日1回15mgから投与を開始することが望ましい。**
(2) 1日1回30mgから45mgに増量した後に浮腫が発現した例が多くみられているので、**45mgに増量する場合には、浮腫の発現に留意すること。**
(3) **インスリンとの併用時**においては、浮腫が多く報告されていることから、**1日1回15mgから投与を開始すること。**本剤を増量する場合は浮腫及び心不全の症状・徴候を十分に観察しながら慎重に行うこと。ただし、1日量として30mgを超えないこと。
(4) 一般に**高齢者**では生理機能が低下しているので、**1日1回15mgから投与を開始することが望ましい。**

OD錠の場合

本剤は口腔内で崩壊するが、口腔粘膜からの吸収により効果発現を期待する製剤ではないため、唾液又は水で飲み込むこと。（「適用上の注意」の項参照）

3. 臨床成績

3－1 臨床データパッケージ

該当しない

3－2 臨床効果

2型糖尿病患者を対象に、1日1回ピオグリタゾンとして15mg、30mg又は45mgを投与した二重盲検比較試験を含む各種臨床試験において、総合血糖改善度が評価された821例の改善率(「中等度改善」以上)は50.8％（417/821例）である。

さらに、長期投与試験（28～48週間以上投与）でも、空腹時血糖及びHbA_{1C}の下降は持続し、作用の減弱はみられず、安定した血糖コントロールが得られている。

なお、下記の治療効果不十分例を対象とした二重盲検比較試験の結果は次のとおりである。

1. 食事療法、運動療法のみの2型糖尿病

1日1回ピオグリタゾンとして30mgを12週間投与した結果、HbA_{1C}値は1.08±1.47％（63例の平均値±標準偏差）の下降が認められている。

2. 食事療法、運動療法に加えてスルホニルウレア剤を使用中の2型糖尿病

1日1回ピオグリタゾンとして30mgを12週間投与した結果、HbA_{1C}値は1.24±1.33％（56例の平均値±標準偏差）の下降が認められている。

3. 食事療法、運動療法に加えてα-グルコシダーゼ阻害剤を使用中の2型糖尿病

1日1回ピオグリタゾンとして30mgを16週間投与した結果、HbA_{1C}値は0.91±0.89％（55例の平均値±標準偏差）の下降が認められている。

4. 食事療法、運動療法に加えてビグアナイド系薬剤を使用中の2型糖尿病

1日1回ピオグリタゾンとして15mgを12週間、その後30mgを16週間投与した結果、HbA_{1C}値は0.67±0.80％（83例の平均値±標準偏差）の下降が認められている。

5. 食事療法、運動療法に加えてインスリン製剤を使用中の2型糖尿病

1日1回ピオグリタゾンとして30mgを16週間投与した結果、HbA_{1C}値は、1.22±1.11％（45例の平均値±標準偏差）の下降が認められている。

3－3 臨床薬理試験：忍容性試験

健康成人男子99例を対象に、ピオグリタゾンとして5mg、15mg、30mg、45mg、60mgあるいはプラセボの単回投与試験、また、15mg（分1）、30mg（分1）、60mg（分1）、60mg（分2）あるいはプラセボの9日間（2日目休薬）反復投与試験を実施した。

その結果、反復投与の60mg投与で12例中4例、30mg投与で6例中1例、プラセボ投与で18例中1例に軽度の肝機能検査異常（AST（GOT）、ALT（GPT）上昇）がみられ、また、一部の例で血中脂質の変動がみられたのみで、その他に特記すべき異常所見は認められず忍容性は良好であり、1日60mg以下の用量で前記Ⅱ相試験を実施することが妥当であると考えられた[1]。

平賀興吾：臨牀と研究　1997，74：1184

注）本剤の承認用法・用量はV-2-1の項参照

3－4　探索的試験：用量反応探索試験

食事療法（一部の症例では併せて運動療法）のみでは効果不十分な2型糖尿病患者188例を対象に、1日1回朝食前又は朝食後にピオグリタゾンとして7.5mg、15mg、30mgあるいはプラセボを8週間経口投与する試験を実施した。

その結果、血糖値、HbA_{1C}及び1, 5-AGからみた血糖コントロールは明らかな用量相関性が認められた（$p<0.01$、回帰分析）。すなわち、30mg群及び15mg群では明らかな有効性が認められ、また、15mg群より30mg群の方がより有効であった。7.5mg群では効果は明らかでなかった。自他覚的副作用は30mg群で12.5％、15mg群で4.5％、7.5mg群で2.1％、プラセボ群で2.1％に発現した。臨床検査値の異常変動は30mg群で10.4％、15mg群で13.6％、7.5mg群で6.4％、プラセボ群で10.6％に発現したが、重篤なものはみられなかった。

以上の結果から、本剤の2型糖尿病に対して至適用量は30mgと考えられたが、15mgでも有効性が認められた[2)]。

兼子　俊男，馬場　茂明，他：臨牀と研究　1997，**74**：1227

3－5　検証的試験

(1) 無作為化平行用量反応試験

1) 食事療法（一部の症例では併せて運動療法）のみでは効果不十分な2型糖尿病患者273例を対象に、1日1回朝食前又は朝食後にピオグリタゾンとして15mg、30mg、45mgあるいはプラセボを12週間経口投与する二重盲検比較試験を実施した。その結果、12週後の空腹時血糖下降度の「中等度改善」以上の改善率は、45mg群59％、30mg群36％、15mg群26％、プラセボ群13％と用量依存的であった。45mg群との比較では、30mg群以下のすべての群との間に有意な差がみられた（$p \leqq 0.001$、Shirley-Williams検定）。総合血糖改善度では、「中等度改善」以上の改善率は、45mg群55％、30mg群39％、15mg群38％、プラセボ群2％と用量依存的であった。45mg群との比較では、30mg群との間には有意差がなく、15mg群及びプラセボ群との間に有意な差がみられた（$p \leqq 0.01$、Shirley-Williams検定）。自他覚的副作用の発現率は、45mg群6.1％、30mg群0％、15mg群4.3％、プラセボ群4.6％であった。臨床検査値の異常変動の発現率は、45mg群15.2％、30mg群11.1％、15mg群7.1％、プラセボ群6.2％であった[3)]。

兼子　俊男，馬場茂明，他：臨牀と研究　1997，**74**：1250

2) 食事療法（一部の症例では併せて運動療法）に加えてSU剤使用で効果不十分な2型糖尿病患者276例を対象に、1日1回朝食前又は朝食後にピオグリタゾンとして15mg、30mg、45mgあるいはプラセボを12週間経口投与する単盲検群間比較試験を実施した。その結果、12週後の空腹時血糖下降度の「中等度改善」以上の改善率は、45mg群60％、30mg群46％、15mg群35％、プラセボ群8％と用量依存的であった。45mg群との比較では、30mg群との間に有意差はなく、15mg群及びプラセボ群との間に有意な差がみられた（$p \leqq 0.01$、Shirley-Williams検定）。総合血糖改善度では、「中等度改善」以上の改善率は、45mg群56％、30mg群56％、15mg群38％、プラセボ群3％と用量依存的であった。45mg群との比較では、30mg群との間には有意差がなく、15mg群及びプラセボ群との間には有意な差がみられた（$p \leqq 0.05$、Shirley-Williams検定）。自他覚的副作用の発現率は、45mg群11.4％、30mg群13.4％、15mg群4.2％、プラセボ群4.6％であった。臨床検査値

の異常変動の発現率は、45mg群17.1％、30mg群11.9％、15mg群4.2％、プラセボ群6.2％であった[4]。

兼子　俊男，馬場茂明，他：臨牀と研究　1997，**74**：1278

以上の結果より、本剤は食事療法、運動療法のみあるいは食事療法、運動療法に加えてSU剤使用で効果不十分な2型糖尿病に対して、1日用量は30mgが中心になると判断されたが、血糖コントロールが不良な患者には45mgも適応になり、さらに、15mg投与でも血糖に対する効果ではプラセボと比較して優れ、一般に生理機能が低下している高齢者等には15mgも選択可能と考えられた[3,4]。

(2) 比較試験

1) 食事療法（一部の症例では併せて運動療法）のみでは効果不十分な2型糖尿病患者152例を対象に、1日1回本剤30mgあるいはプラセボを12週間経口投与する二重盲検比較対照試験を実施した。その結果、本剤はプラセボ群に比べて総合血糖改善度は有意に優れ（$p \leqq 0.001$、2標本Wilcoxon検定）、HbA_{1C}は4週以降有意に低下した（$p \leqq 0.01$、2標本t検定）。自他覚的副作用は、本剤16.9％、プラセボ群6.7％に発現し、臨床検査値の異常変動は、本剤13.0％、プラセボ群10.7％に発現した[5]。

兼子　俊男，馬場茂明，他：臨牀と研究　1997，**74**：1491

2) 食事療法（一部の症例では併せて運動療法）に加えてSU剤使用で効果不十分な2型糖尿病患者149例を対象に、1日1回本剤30mgあるいはプラセボを12週間経口投与する二重盲検比較対照試験を実施した。その結果、本剤はプラセボ群に比べて総合血糖改善度は有意に優れ（$p \leqq 0.001$、2標本Wilcoxon検定）、HbA_{1C}は4週以降有意に低下した（$p \leqq 0.01$、2標本t検定）。自他覚的副作用は、本剤10.5％、プラセボ群6.8％に発現し、臨床検査値の異常変動は、本剤18.4％、プラセボ群8.2％に発現した[6]。

兼子　俊男，馬場茂明，他：臨牀と研究　1997，**74**：1515

3) 食事療法（一部の症例では併せて運動療法）に加えてα-グルコシダーゼ阻害剤使用で効果不十分な2型糖尿病患者130例を対象に、1日1回本剤30mgあるいはプラセボを16週間経口投与する二重盲検比較対照試験を実施した。その結果、本剤はプラセボ群に比べて空腹時血糖は4週以降有意に下降し（$p \leqq 0.01$、2標本t検定）、HbA_{1C}は8週以降有意に下降した（$p \leqq 0.05$、2標本t検定）。自他覚的副作用は、本剤23.4％、プラセボ群7.9％に認められ、臨床検査値の異常変動は、本剤25.0％、プラセボ群23.8％に発現した。

（承認時資料：2002年6月）

4) 食事療法（一部の症例では併せて運動療法）に加えてビグアナイド系薬剤（メトホルミン）使用で効果不十分な2型糖尿病患者173例を対象に、1日1回本剤15mgを12週間、その後30mgを16週間あるいはプラセボを28週間経口投与する二重盲検比較対照試験を実施した。そり結果、本剤はプラセボ群に比べて空腹時血糖値及びHbA_{1C}を4週以降有意に下降した（$p \leqq 0.05$、2標本t検定）。因果関係が否定されなかった有害事象（臨床検査値の異常変動を含む）は、本剤15.7％、プラセボ群11.6％に認められた。

（承認時資料：2008年12月）

5）食事療法（一部の症例では併せて運動療法）に加えてインスリン製剤使用で効果不十分な2型糖尿病患者121例を対象に、1日1回本剤30mgあるいはプラセボを16週間経口投与する二重盲検比較対照試験を実施した。その結果、本剤は投与開始時と比べて空腹時血糖値は4週、12週及び16週（$p < 0.01$、1標本t検定）でHbA_{1C}は4週以降有意に下降した（$p < 0.001$、1標本t検定）。因果関係が否定されなかった有害事象（臨床検査値の異常変動を含む）は、本剤66.7％、プラセボ群44.3％に認められた。

（承認時資料：2009年3月）

（3）安全性試験

長期投与試験

食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤使用で効果不十分な2型糖尿病患者250例を対象に、1日1回本剤30mgより投与を開始し、症状により15mgへの減量あるいは45mgへの増量を可能とし、48週間以上投与した結果、空腹時血糖及びHbA_{1C}は4週以降有意に下降し（$p \leqq 0.01$、1標本t検定）、安定した血糖コントロールが得られた。

自他覚的副作用は248例中45例（18.1％）に発現し、臨牀検査値の異常変動は248例中47例（19.0％）に発現した[7)]。

兼子俊男，馬場茂明，他：臨牀と研究　1997，**74**：1557

3－6　治療的使用

（1）使用成績調査・特定使用成績調査（特別調査）・製造販売後臨床試験（市販後臨床試験）

「本剤の有効性・安全性等について特に問題はない」とされ、「承認、効能・効果、用法・用量に変更はない」とされた（再審査結果通知：2009年12月21日）

（2）承認条件として実施予定の内容又は実施した試験の概要

該当しない

Ⅵ：薬効薬理に関する項目

1. 薬理学的に関連ある化合物又は化合物群

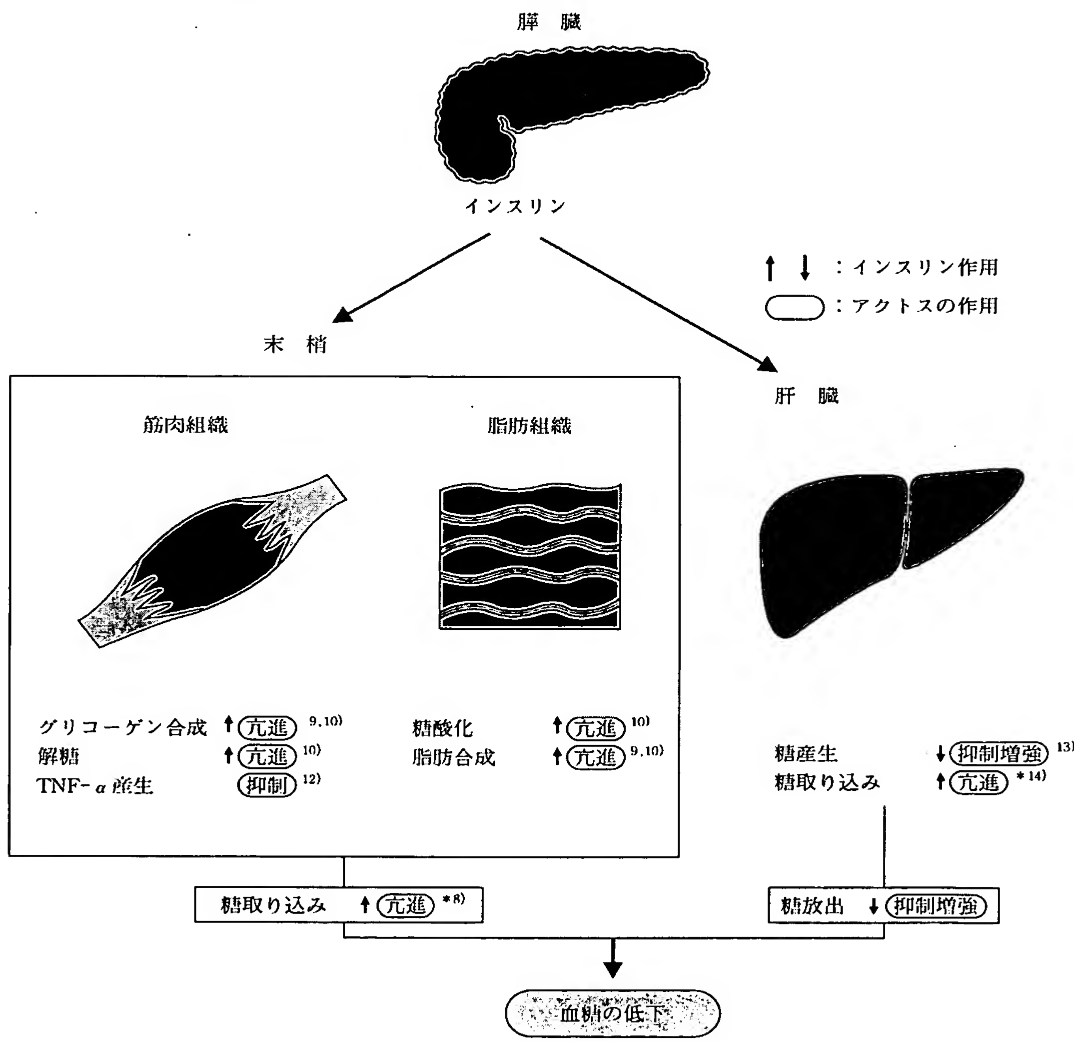
チアゾリジン誘導体

2. 薬理作用

2－1 作用部位・作用機序

ピオグリタゾンは末梢（筋肉組織、脂肪組織）及び肝臓におけるインスリン抵抗性を改善することにより、末梢では糖の取り込み及び糖の利用を促進し、肝臓では糖の放出を抑制して血糖を低下させる。

■インスリン抵抗性改善作用を示すアクトスの作用点



※この作用は臨床試験で認められている。

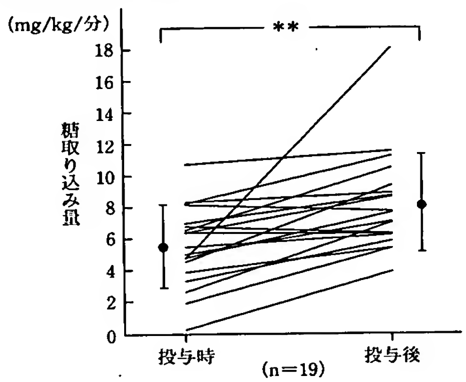
2－2　薬効を裏付ける試験成績

(1) 末梢組織におけるインスリン抵抗性改善作用

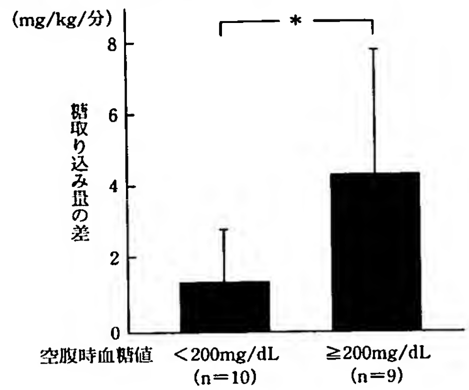
1) 糖取り込み促進作用

アクトス投与により、末梢での糖の取り込み量が有意に増加した。また、アクトス投与前の空腹時血糖値が200mg/dL以上の例では、200mg/dL未満の例よりも糖の取り込みが有意に増加した[8]。

■糖取り込み作用



■空腹時血糖値別の糖取り込み作用



平均値±標準偏差　Student's paired t-test あるいは Wilcoxon's順位和検定、＊＊：p≦0.01、＊：p≦0.05

［試験方法］

対象患者：食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤を使用中の2型糖尿病患者で、空腹時血糖が150mg/dL以上の症例。

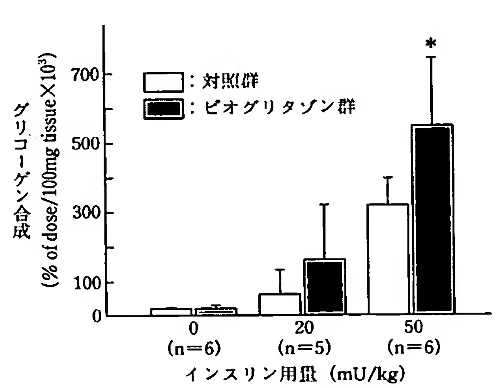
投与法：アクトス1日1回30mgを3カ月間投与した。

測定法：正常血糖高インスリンクランプ法を用いて末梢の糖取り込みを算出した。

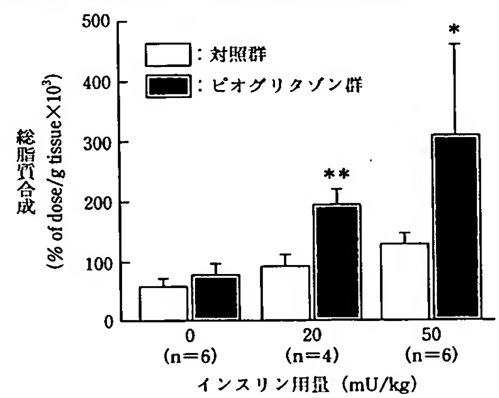
2) 糖取り込み促進作用（マウス）

肥満型糖尿病であるKKA^{y}マウスの横隔膜及び脂肪組織において、ピオグリタゾンは非投与対照群に比べて外来性インスリン刺激による糖の取り込みを有意に増加した[9]。

■横隔膜での糖取り込み促進作用



■脂肪組織での糖取り込み促進作用



平均値±標準偏差　対照群の相当する値に対してStudentのt検定　＊＊：p＜0.01、＊：p＜0.05

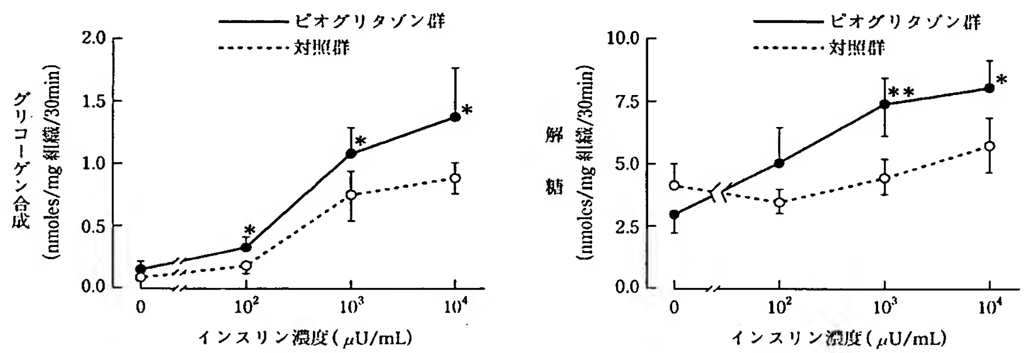
［試験方法］

KKA^{y}マウス（10～11週齢雄性）にピオグリタゾンを4日間混餌（10mg/100g飼料）し、20時間絶食後グルコース-U-^{14}C（2μCi/マウス）とインスリンを投与した後、横隔膜及び副睾丸周囲脂肪組織を取り出し、それぞれグリコーゲン画分及び総脂肪画分へのグルコース-U-^{14}C取り込みを測定した。

3）グリコーゲン合成及び解糖亢進作用（ラット）

肥満型糖尿病であるWistar fattyラットのヒラメ筋において、ピオグリタゾンは非投与対照群に比べて外来性インスリンのグリコーゲン合成及び解糖亢進を有意に増加した[10)]。

■グリコーゲン合成亢進作用　　**■解糖亢進作用**



平均値±標準偏差（n＝5）
対照群の相当する値に対してStudentのt検定　＊＊：$p < 0.001$、＊：$p < 0.05$

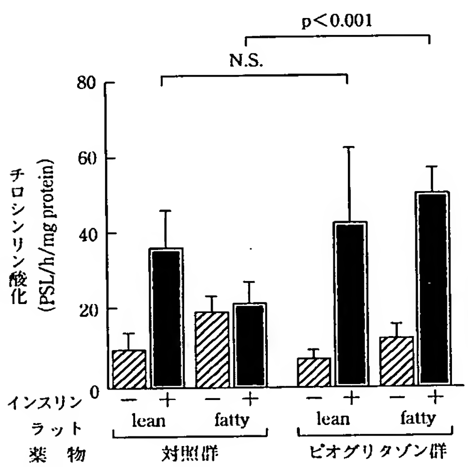
［試験方法］

Wistar fattyラット（6週齢雄性）にピオグリタゾン（3mg/kg/日）を10日間経口投与した後、後肢ヒラメ筋を単離してグルコース、グルコース-5-^{3}H及び種々の濃度のインスリンとインキュベーションし、グリコーゲン合成と解糖系の指標である^3H_2Oの生成を調べた。

4）インスリンの細胞内情報伝達機構の改善作用（ラット）

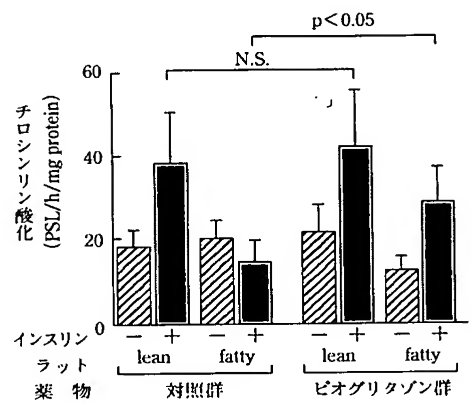
Wistar fatty ラットの骨格筋において、ピオグリタゾンはグルコース取り込み、グリコーゲン合成などに関係するインスリン受容体（IRs）・インスリン受容体基質（IRS-1）のリン酸化、及びその後のシグナル伝達に関与するPI3（ホスファチジルイノシトール3）キナーゼ活性が低下しているのを正常化した。一方、正常ラット（lean ラット）では影響は認められなかった[11]。

■インスリン受容体（IRs）のリン酸化に及ぼす影響



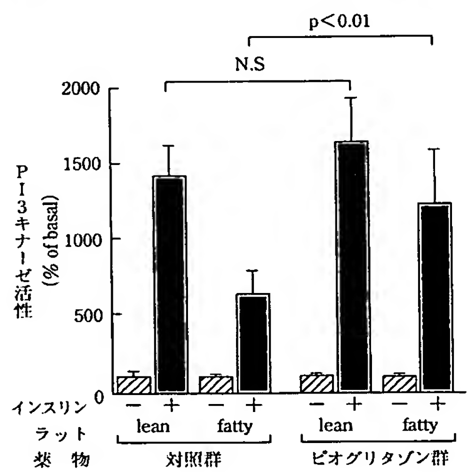
平均値±標準偏差（n＝6）、Studentのt検定

■インスリン受容体基質（IRS-1）のリン酸化に及ぼす影響



平均値±標準偏差（n＝6）、Studentのt検定

■PI 3キナーゼ活性化に及ぼす影響



平均値±標準偏差（n＝4～6）、Studentのt検定

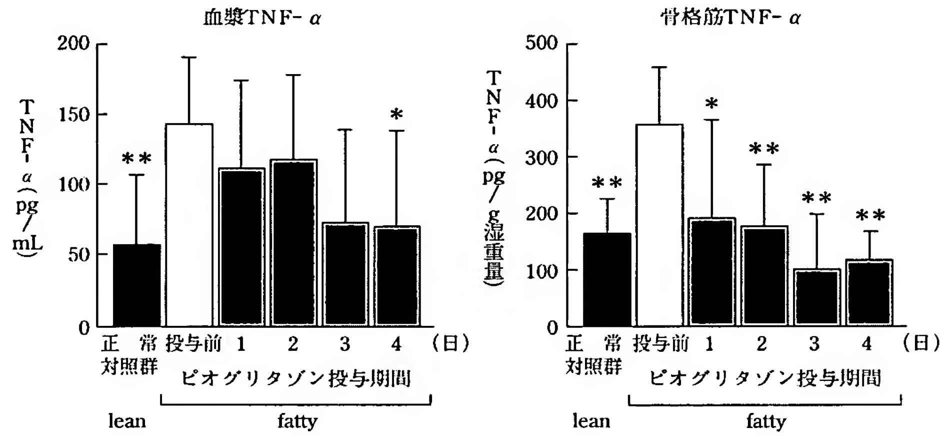
［試験方法］

Wistar fatty ラット（6週齢雄性）にピオグリタゾン（3mg/kg/日）を10日間経口投与した後、18時間絶食させ、インスリン投与して骨格筋を採取し、IRsおよびIRS-1のリン酸化、PI 3キナーゼ活性を測定した。一方、正常群（lean ラット）には本薬の10mg/kg/日を投与し同様に検討した。

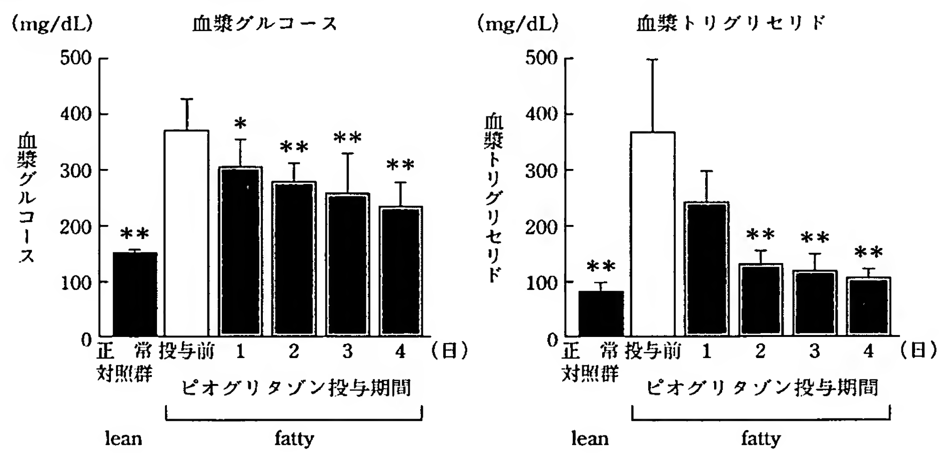
5）TNF-αの低下作用（ラット）

Wistar fattyラットにおいて、ピオグリタゾンはインスリン受容体基質に影響し、糖の取り込みなどを抑制するTNF-αを有意に低下させ、これと並行して血漿グルコース、トリグリセリドも有意に減少させた[12)]。

■血漿及び骨格筋TNF-αの低下作用



■血漿グルコース及び血漿トリグリセリド低下作用



平均値±標準偏差（n＝9、10）

fattyラット（投与前）に対してDunnett検定　**：$p < 0.01$、*：$p < 0.05$

［試験方法］

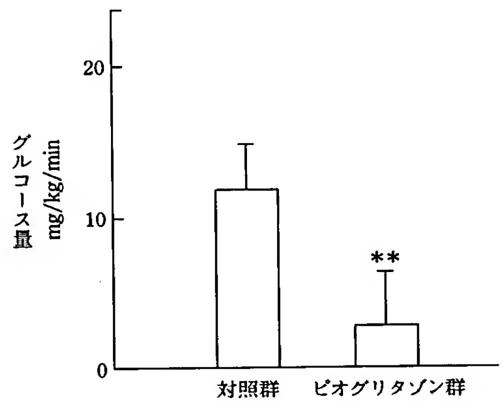
Wistar fattyラット（16週齢雄性）を、ピオグリタゾン投与前、ピオグリタゾン3mg/kg/日の経口投与1、2、3、4日後に屠殺した。無投与の同齢雄性leanラットを正常対照群として、血漿及び骨格筋のTNF-α、血漿グルコース、トリグリセリドを測定した。

(2) 肝臓におけるインスリン抵抗性改善作用

1) 糖産生抑制作用（ラット）

Wistar fatty ラットにおいて、ピオグリタゾンは肝臓での糖の産生を有意に抑制した[13)]。

■肝からの糖産生に対する作用



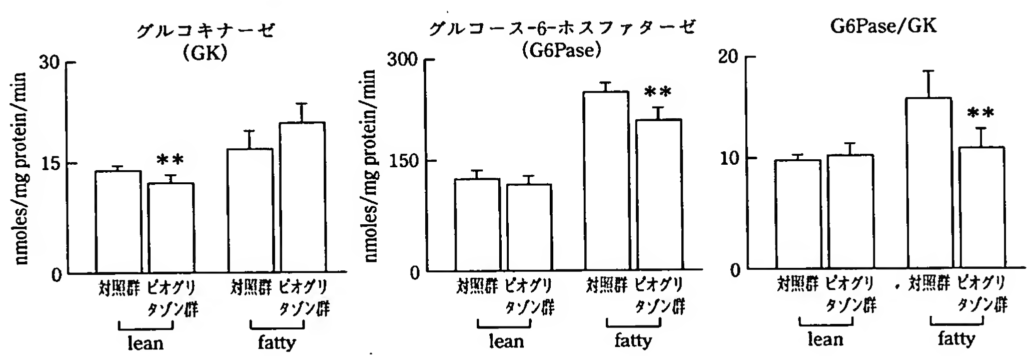
［試験方法］
Wistar fatty ラット（11週齢雄性）にピオグリタゾン 3mg/kg/日を7日間経口投与し、Terrettaz & Jeanrenaud 法に準じて非絶食下でグルコースクランプを行い、肝からの糖産生を測定した。

平均値±標準偏差（n＝5～6）、Student の t 検定　**：p＜0.01

2) 糖産生に関与する肝酵素への作用（ラット）

Wistar fatty ラットにおいて、ピオグリタゾンは糖産生にかかわるグルコース-6-ホスファターゼ（G6Pase）の活性を低下させ、その逆の作用を有するグルコキナーゼ（GK）の活性を亢進した。また G6Pase/GK 値は正常対照（lean ラット）のレベルまで低下し、肝臓全体の糖代謝が是正された[13)]。

■肝における糖代謝関連酵素に対する作用



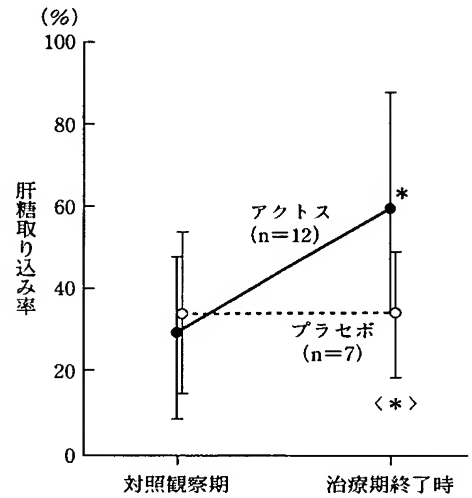
平均値±標準偏差（n＝5）、各群の対照群の相当する値に対して Student の t 検定　**：p＜0.01

［試験方法］
Wistar fatty ラット（11週齢雄性）にピオグリタゾン 3mg/kg/日を7日間経口投与後、肝臓をホモジナイズし、糖代謝関連酵素活性を測定した。
正常対照として同週齢の Wistar lean ラットに本薬 10mg/kg を投与し、同様に関連酵素活性を測定した。

3）肝での糖取り込み促進作用

アクトス投与により、肝での糖の取り込み率がプラセボ群に比べて有意に上昇した[14]。

■糖取り込み作用



平均値±標準偏差　1標本t検定　〈　〉内は群間比較（2標本t検定）　＊：p≦0.05

［試験方法］

対象患者：食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤を使用中の2型糖尿病患者で、観察期間中の空腹時血糖が120～159mg/dL、HbA_{1C}値の変動が1％以内の症例。

投与法：アクトス1日1回朝食前又は朝食後に30mgを12週間投与した。

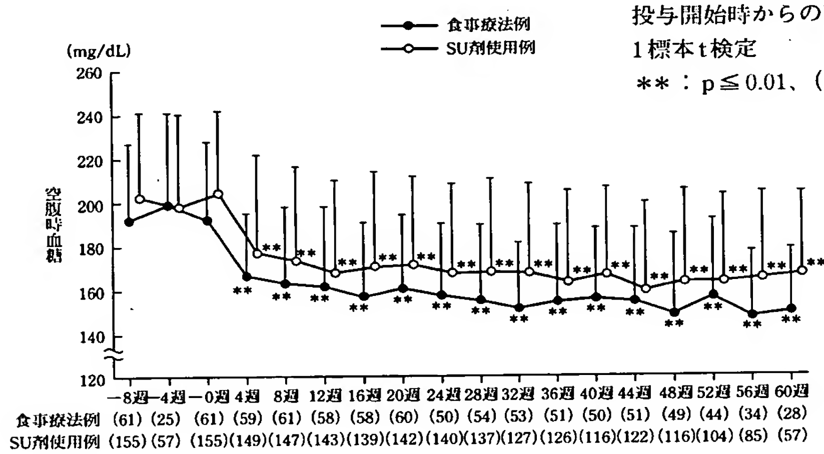
測定法：正常血糖高インスリンクランプ下にブドウ糖を経口負荷する手法（clamp-OGL試験）を用いて肝糖取り込み率を算出した。

(3) 空腹時血糖値及びHbA1c低下作用

アクトス投与により、空腹時血糖値及びHbA1cはいずれも4週目より有意に低下し、1年以上安定した推移を示した[7]。

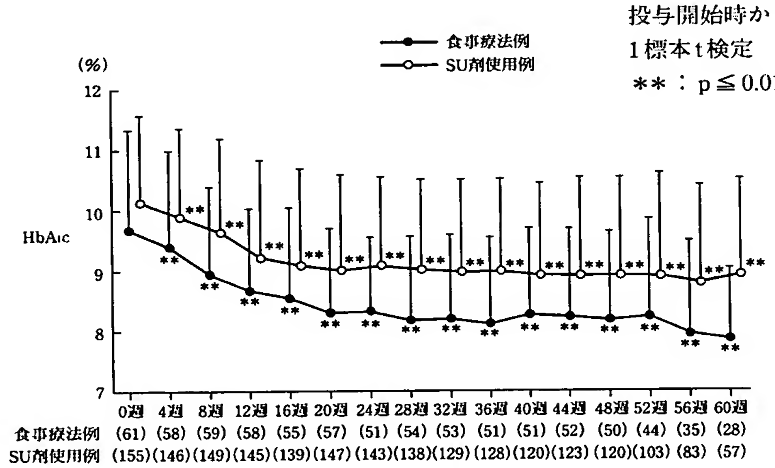
■空腹時血糖の推移

平均値±標準偏差
投与開始時からの変化量に対して
1標本t検定
＊＊：p≦0.01、（ ）内は症例数



■HbA1cの推移

平均値±標準偏差
投与開始時からの変化量に対して
1標本t検定
＊＊：p≦0.01、（ ）内は症例数



［試験方法］

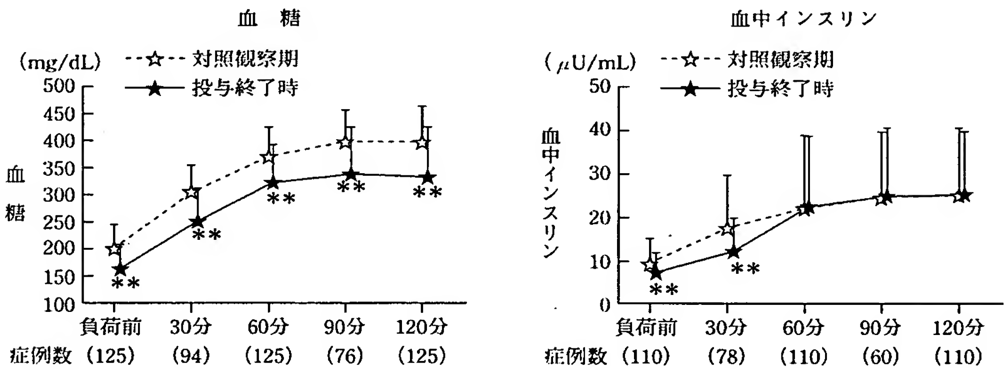
対象患者：食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤使用中の2型糖尿病患者で、観察期開始時及び終了時の空腹時血糖がいずれも150mg/dL以上、かつこれら2回の空腹時血糖の変化量が30mg/dL以内の患者250例（食事療法群70例、SU使用群180例）

投与法：アクトス1日1回30mgを朝食前又は朝食後に、原則として48週間以上投与した。

(4) 経口ブドウ糖負荷試験

アクトス投与により75g経口ブドウ糖負荷前及び負荷後の血糖値は、観察期に比べていずれも有意な低下を示した。また、血中インスリン値は糖負荷前及び負荷後30分に有意に低下したが、その後はほぼ同様に推移した[7]。

■75g経口ブドウ糖負荷試験



平均値±標準偏差、対照観察期に相当する値に対して　1標本t検定、＊＊：p≦0.01

［試験方法］

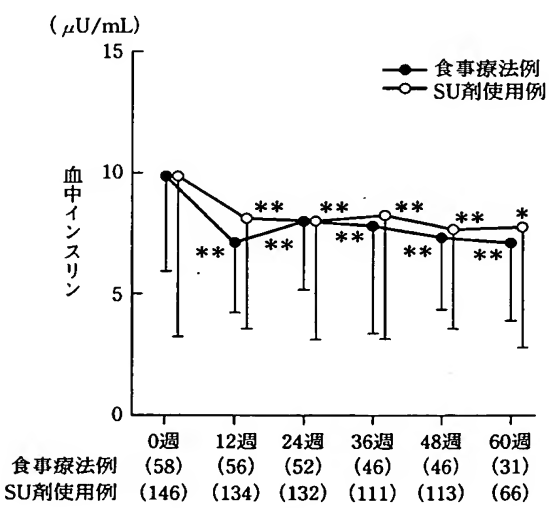
対象患者：食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤使用中の2型糖尿病患者で、観察期開始時及び終了時の空腹時血糖がいずれも150mg/dL以上、かつこれら2回の空腹時血糖の変化量が30mg/dL以内の症例。

投 与 法：アクトス1日1回30mgを朝食前又は朝食後に、原則として48週以上投与した。

(5) 空腹時血中インスリン値に対する作用

空腹時血中インスリン値は、食事療法例及びSU剤使用例ともにアクトス投与後12週から60週まで有意な低下を示した[7]。

■血中インスリン値の推移



［試験方法］

対象患者：食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤使用中の2型糖尿病患者で、観察期開始時及び終了時の空腹時血糖がいずれも150mg/dL以上、かつこれら2回の空腹時血糖の変化量が30mg/dL以内の症例。

投 与 法：アクトス1日1回30mgを朝食前又は朝食後に、原則として48週間以上投与した。

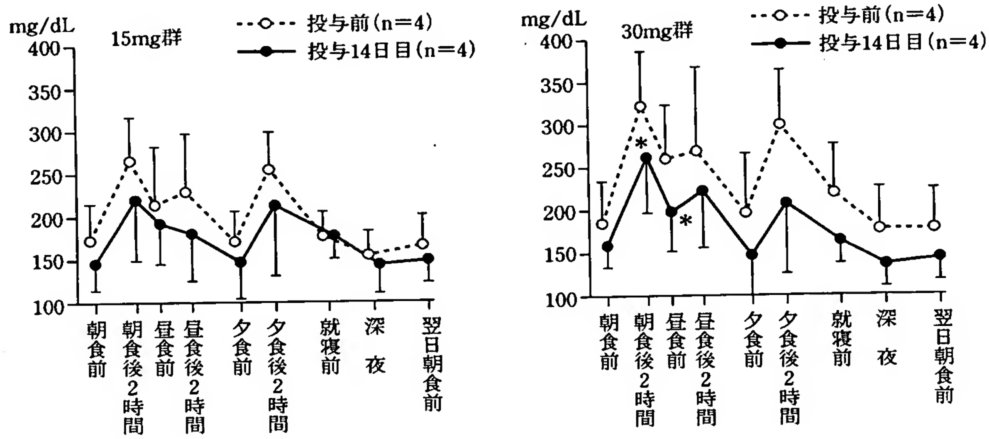
平均値±標準偏差、投与開始時からの変化量に対して　1標本t検定、＊＊：p≦0.01、＊：p≦0.05

（　）内は症例数

(6) 血糖の日内変動に及ぼす影響

アクトス投与開始前と比べて投与後の血糖値は15mg投与では就寝前を除いて低値を示し、30mg投与ではすべての時点で低値を示した。また、血糖の変動メルクマールであるM値及び血糖曲線下面積は15mg、30mg投与ともに改善した[15)]。

■血糖の日内変動



平均値±標準偏差、投与前の相当する値に対して1標本t検定　＊：p≦0.05

■血糖日内変動のM値及び血糖曲線下面積

	群	例数	投与前	投与後	下降率	
M値	30mg群	4	48.0±29.5	24.6±15.3	45.6±25.2	＊
	15mg群	4	26.3±18.2	18.0±13.9	34.8± 6.6	＊
血糖曲線下面積 (mg・hr/dL)	30mg群	4	5884±1445	4635±1057	19.8±15.7	NS
	15mg群	4	4912±1079	4400± 967	10.3± 5.5	＊

注）平均値±標準偏差　検定；1標本t検定　＊：p≦0.05，NS：p＞0.05

［試験方法］

対象患者：食事療法（一部の症例では併せて運動療法）中の2型糖尿病患者で、空腹時血糖が150mg/dL以上、かつ安定している症例。

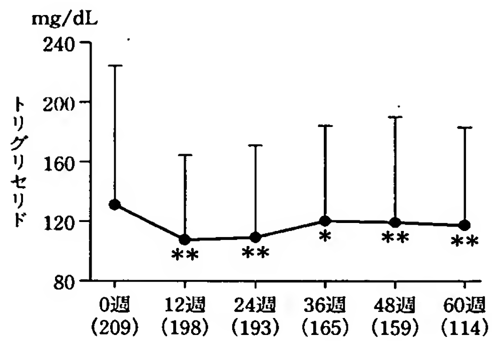
投与法：アクトス1日1回15mg又は30mgを朝食後に、14日間投与した。

(7) その他の作用

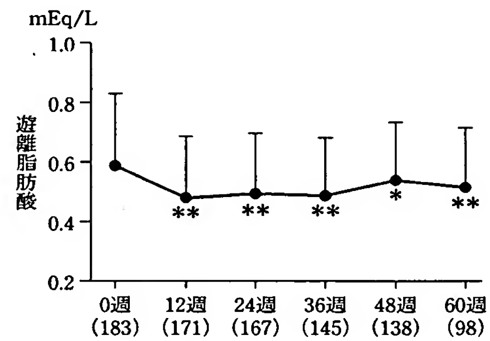
1) 脂質代謝に及ぼす影響

アクトス投与により、トリグリセリド及び遊離脂肪酸は12週目より有意に低下した。HDLコレステロール及び総コレステロールはそれぞれ12週目と24週目より有意に上昇した[7]。

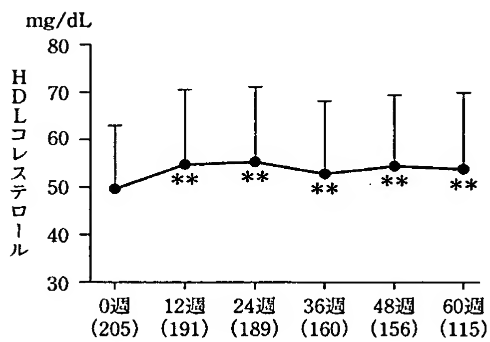
■トリグリセリド



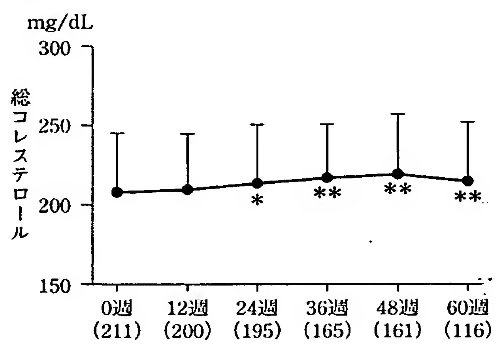
■遊離脂肪酸



■HDLコレステロール



■総コレステロール



平均値±標準偏差、投与開始時からの変化量に対して　1標本t検定、**：$p \leqq 0.01$、*：$p \leqq 0.05$
(　　) 内は症例数

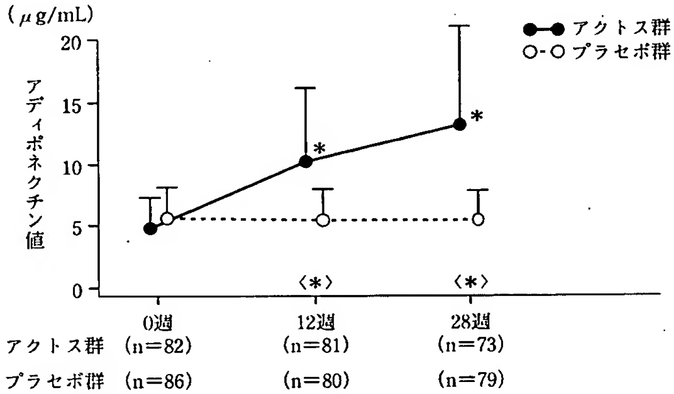
[試験方法]

対象患者：食事療法（一部の症例では併せて運動療法）のみあるいは食事療法（一部の症例では併せて運動療法）に加えてSU剤使用中の2型糖尿病患者で、観察期開始時及び終了時の空腹時血糖がいずれも150mg/dL以上、かつこれら2回の空腹時血糖の変化量が30mg/dL以内の症例。

投与法：アクトス1日1回30mgを朝食前又は朝食後に、原則として48週間以上投与した。

2) アディポネクチンに及ぼす影響
アクトス投与により、アディポネクチンは有意に上昇した。

■アディポネクチンの推移



平均値±標準偏差、( ) 内の数字は症例数
投与開始時からの変化量に対する検定、群内は1標本t検定、群間は2標本t検定〈 〉で示した。
＊：$p<0.05$

［試験方法］
対象患者：食事療法（一部の症例では併せて運動療法）に加えてビグアナイド系薬剤（メトホルミン）使用中の2型糖尿病患者で、観察期間開始8週後のHbA_{1C}が6.5～10.0％で、観察期間開始4週後と8週後のHbA_{1C}の差が、4週後のHbA_{1C}値の10.0％以内の症例（173例）。
投 与 法：アクトス群（84例）は15mgを1日1回12週間投与後、忍容性に問題がない場合は1日1回30mgを16週間投与した。プラセボ群（89例）は28週間プラセボを投与した。
（承認資料：2008年12月）

2－3 作用発現時間・持続時間

該当資料なし

Ⅶ：薬物動態に関する項目

1. 血中濃度の推移・測定法

1－1　治療上有効な血中濃度

該当資料なし

1－2　最高血中濃度到達時間

Ⅶ－1－3 の項参照

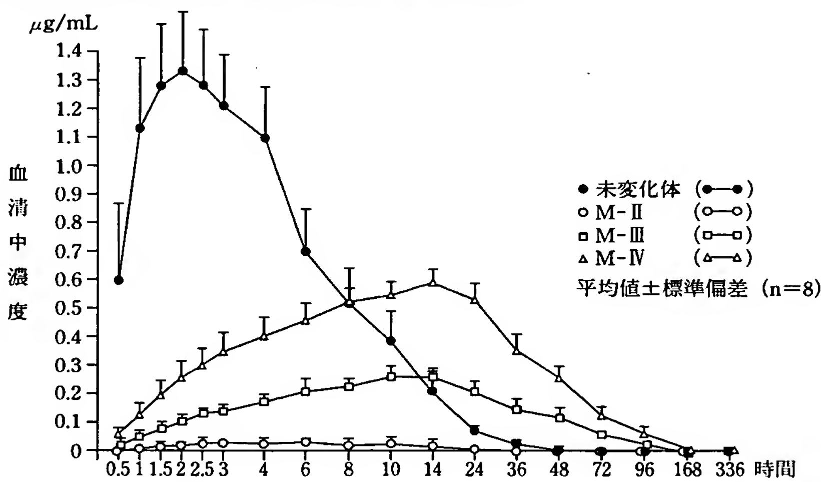
1－3　臨床試験で確認された血中濃度

（1）単回投与での検討（健康成人）

1）30mg 投与での検討

健康成人男子 8 例を対象に、ピオグリタゾンとして 30mg を朝絶食時に単回経口投与したとき、血中には未変化体及び代謝物（M－Ⅱ～Ⅴ、49 頁参照）が検出された。未変化体及び活性代謝物（M－Ⅱ～Ⅳ）の血清中濃度の推移は下記のとおりであった。

■未変化体及び活性代謝物の血清中濃度の推移



■未変化体及び活性代謝物のパラメータ

化合物	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-336h} (μg・h/mL)	$t_{1/2}$ (h)
未変化体	1.4 ± 0.2	1.8 ± 0.4	11.6 ± 2.2	5.4 ± 1.7
M－Ⅱ	0.04 ± 0.02	4.8 ± 2.5	0.4 ± 0.3	—
M－Ⅲ	0.3 ± 0.0	11.5 ± 2.1	12.8 ± 2.1	25.0 ± 4.7
M－Ⅳ	0.6 ± 0.1	14.8 ± 4.0	29.5 ± 4.5	23.8 ± 2.7

平均値±標準偏差（n＝8）

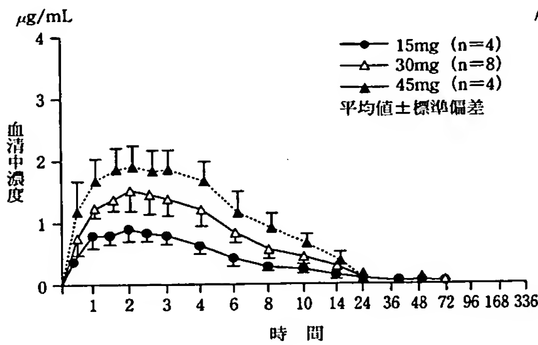
（承認時資料集計：1999 年 9 月）

2) 15mg～45mg 投与での検討

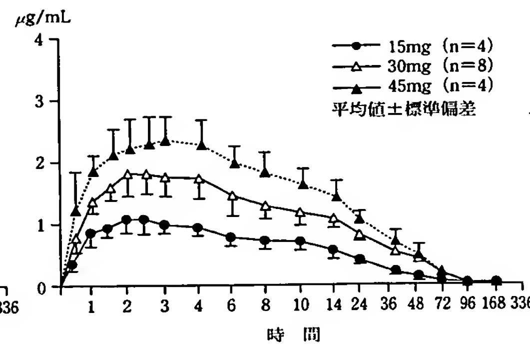
健康成人を対象に、ピオグリタゾンとして 15mg、30mg あるいは 45mg を朝絶食時に単回経口投与したとき、未変化体及び活性化合物合計（未変化体＋活性代謝物 M－Ⅱ～Ⅳ）の血清中濃度の推移は下記のとおりであった[1]。

■未変化体及び活性化合物合計の血清中濃度の推移

未 変 化 体



活性化合物合計



■未変化体及び活性化合物合計のパラメータ

化合物	投与量 (mg)	例数	C_{max} (μg/mL)	T_{max} (h)	AUC[1] (μg・h/mL)	$t_{1/2}$ (h) α	$t_{1/2}$ (h) β	MRT[2] (h)
未変化体	15	4	0.9 ± 0.2	1.6 ± 0.5	6.5 ± 1.0	5.0 ± 0.6		7.1 ± 1.2
						3.0 (n = 1)	7.0 (n = 1)	
	30	8	1.5 ± 0.3	1.9 ± 0.5	13.9 ± 3.1	2.9 ± 0.6	7.9 ± 1.7	10.3 ± 2.2
	45	4	1.9 ± 0.4	2.4 ± 0.8	18.3 ± 4.9	3.5 ± 1.4	6.2 ± 1.0	8.4 ± 1.1
活性化合物合計	15	4	1.1 ± 0.2	2.3 ± 0.3	26.2 ± 2.1	15.4 ± 3.4		27.1 ± 2.6
	30	8	1.9 ± 0.4	2.3 ± 0.4	57.7 ± 9.3	20.4 ± 3.1		32.6 ± 3.6
	45	4	2.4 ± 0.4	2.9 ± 0.9	75.6 ± 16.7	20.3 ± 1.5		36.6 ± 3.5

1) 15 mg は $AUC_{0\text{-}168h}$、30～45 mg は $AUC_{0\text{-}336h}$

2) 15 mg は $MRT_{0\text{-}168h}$、30～45 mg は $MRT_{0\text{-}336h}$

平均値±標準偏差

■30mg 投与時の未変化体及び血清中代謝物の AUC

化合物	$AUC_{0\text{-}336h}$ (μg・h/mL)
未変化体	13.9 ± 3.1
M－Ⅰ	検出されず
M－Ⅱ	0.4 ± 0.3
M－Ⅲ	12.1 ± 2.8
M－Ⅳ	31.2 ± 4.5
M－Ⅴ	1.9 ± 0.4

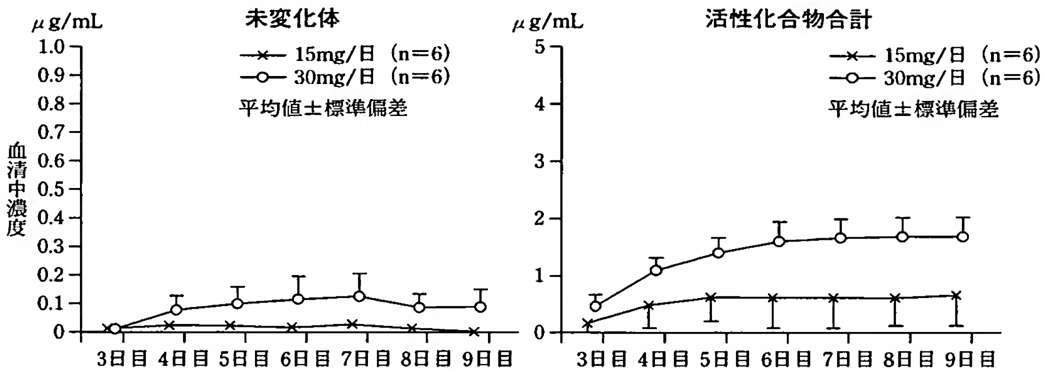
平均値±標準偏差（n＝8）

(2) 反復投与での検討

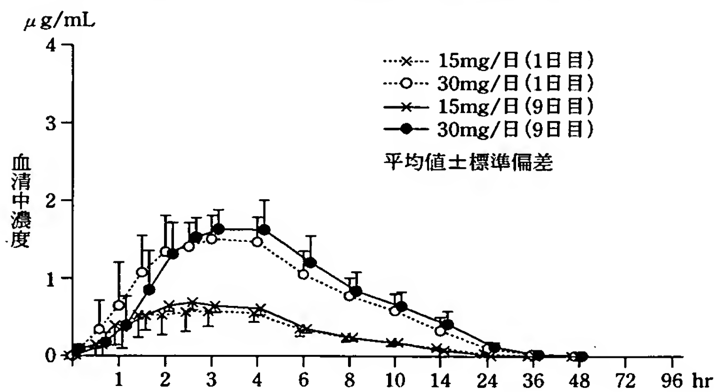
1) 健康成人での検討

健康成人を対象に、ピオグリタゾンとして 15mg あるいは 30mg を 1 日 1 回、1 日目及び 3〜9 日目のそれぞれ朝食後に経口投与したとき、血清中の未変化体及び活性化合物合計 C_{min}（トラフ濃度）は、6〜7 日目にはほぼ定常状態に達していた。また、未変化体の血清中濃度の推移は 1 日目と 9 日目では、大きな変化はなかった[1]。

■血清中未変化体及び活性化合物合計の C_{min} の推移



■第 1 日目と第 9 日目の血清中未変化体濃度の推移



■未変化体及び活性化合物合計のパラメータ

化合物	投与条件	例数	日数	C_{max} (μg/mL)	T_{max} (h)	AUC[1] (μg・h/mL)	$t_{1/2}$ (h) α	$t_{1/2}$ (h) β	MRT[2] (h)
未変化体	15mg/日	6	1日目	0.7 ± 0.2	2.3 ± 1.1	5.2 ± 0.7	4.4 ± 1.0 1.8 (n = 1)	6.6 (n = 1)	8.0 ± 2.1
			9日目	0.7 ± 0.1	2.5 ± 0.9	4.8 ± 0.4	3.3 ± 0.4		5.9 ± 0.4
	30mg/日	6	1日目	1.7 ± 0.3	2.9 ± 1.2	14.9 ± 4.5	4.9 ± 1.3		8.4 ± 1.6
			9日目	1.7 ± 0.3	3.0 ± 0.5	15.3 ± 4.0	4.9 ± 0.9		7.7 ± 0.7
活性化合物合計	15mg/日	6	1日目	0.9 ± 0.2	3.7 ± 1.3	19.9 ± 2.5	18.6 ± 4.1		18.0 ± 1.4
			9日目	1.5 ± 0.1	3.1 ± 1.1	22.6 ± 1.4	16.2 ± 2.8		10.2 ± 0.1
	30mg/日	6	1日目	2.1 ± 0.2	3.3 ± 1.0	49.0 ± 7.5	17.4 ± 2.3		18.2 ± 0.9
			9日目	3.4 ± 0.5	3.7 ± 1.3	57.5 ± 10.3	20.5 ± 6.0		10.8 ± 0.3

1) 第 1 日目は AUC_{0-48h}、第 9 日目は AUC_{0-24h}

2) 第 1 日目は MRT_{0-48h}、第 9 日目は MRT_{0-24h}

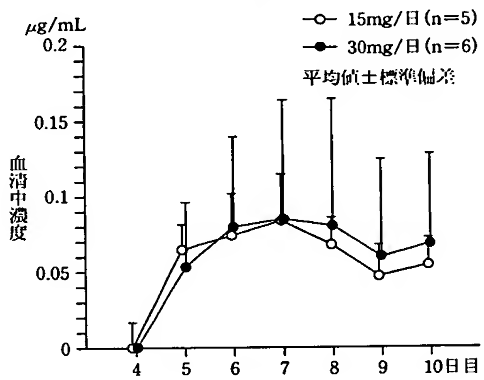
平均値±標準偏差

2）高齢健常者での検討

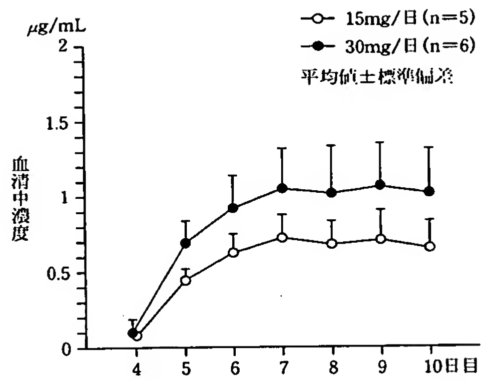
高齢健常者を対象に、ピオグリタゾンとして15mgあるいは30mgを1日1回、1日目及び4～10日目のそれぞれ朝食後に経口投与したとき、未変化体及び活性化合物合計のC_{min}は、6～7日目にほぼ定常状態に達していた[16)]。

■血清中未変化体及び活性化合物合計のC_{min}の推移

未変化体



活性化合物合計



■未変化体及び活性化合物合計のパラメータ

<table>
<tr><th rowspan="2">化合物</th><th rowspan="2">投与条件</th><th rowspan="2">例数</th><th rowspan="2">日数</th><th rowspan="2">C_{max} (μg/mL)</th><th rowspan="2">T_{max} (h)</th><th rowspan="2">AUC[1)] (μg·h/mL)</th><th colspan="2">$t_{1/2}$ (h)</th><th rowspan="2">MRT[2)] (h)</th></tr>
<tr><th>α</th><th>β</th></tr>
<tr><td rowspan="6">未変化体</td><td rowspan="3">15mg/日</td><td rowspan="3">5</td><td rowspan="2">1日目</td><td rowspan="2">0.6±0.2</td><td rowspan="2">5.6±3.3</td><td rowspan="2">5.3±1.5</td><td colspan="2">4.1±1.3</td><td rowspan="2">11.0±3.4</td></tr>
<tr><td>1.9 (n=1)</td><td>12.3 (n=1)</td></tr>
<tr><td>10日目</td><td>0.7±0.1</td><td>4.8±1.8</td><td>6.0±0.7</td><td colspan="2">4.9±1.0</td><td>8.8±1.1</td></tr>
<tr><td rowspan="3">30mg/日</td><td rowspan="3">6</td><td rowspan="2">1日目</td><td rowspan="2">1.0±0.3</td><td rowspan="2">3.2±0.8</td><td rowspan="2">7.6±1.7</td><td>2.2±1.2</td><td>6.3±1.4</td><td rowspan="2">8.4±2.7</td></tr>
<tr><td colspan="2">2.3 (n=1)</td></tr>
<tr><td>10日目</td><td>1.2±0.2</td><td>3.7±1.4</td><td>10.2±1.4</td><td colspan="2">4.0±0.9</td><td>7.2±1.2</td></tr>
<tr><td rowspan="4">活性化合物合計</td><td rowspan="2">15mg/日</td><td rowspan="2">5</td><td>1日目</td><td>0.8±0.2</td><td>6.0±2.8</td><td>20.7±3.4</td><td colspan="2">20.8±4.0</td><td>25.4±3.2</td></tr>
<tr><td>10日目</td><td>1.4±0.2</td><td>5.2±2.7</td><td>23.3±3.3</td><td colspan="2">17.0±2.6</td><td>11.4±0.5</td></tr>
<tr><td rowspan="2">30mg/日</td><td rowspan="2">6</td><td>1日目</td><td>1.5±0.4</td><td>3.5±0.8</td><td>33.9±7.7</td><td colspan="2">18.3±5.9</td><td>22.3±2.5</td></tr>
<tr><td>10日目</td><td>2.5±0.3</td><td>3.8±1.2</td><td>39.7±7.0</td><td colspan="2">17.8±3.8</td><td>10.7±0.5</td></tr>
</table>

平均値±標準偏差

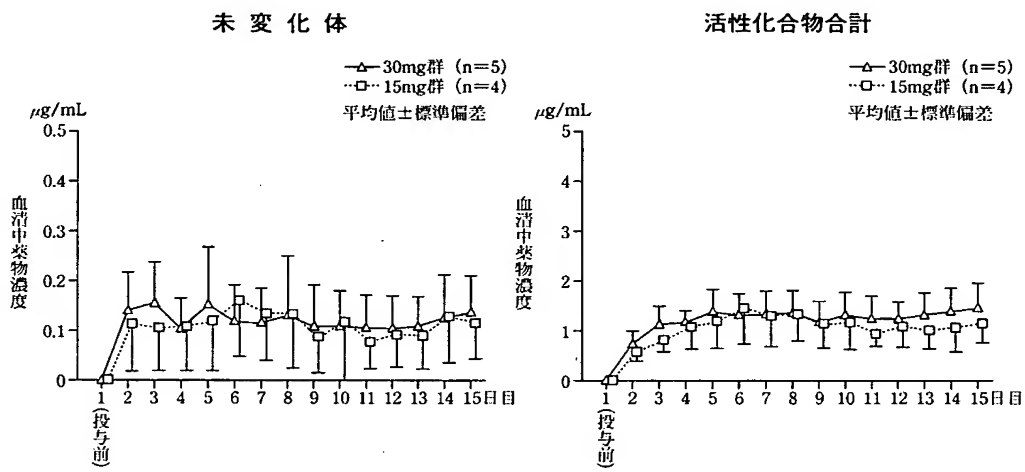
1）第1日目はAUC_{0-72h}、第10日目はAUC_{0-24h}

2）第1日目はMRT_{0-72h}、第10日目はMRT_{0-24h}

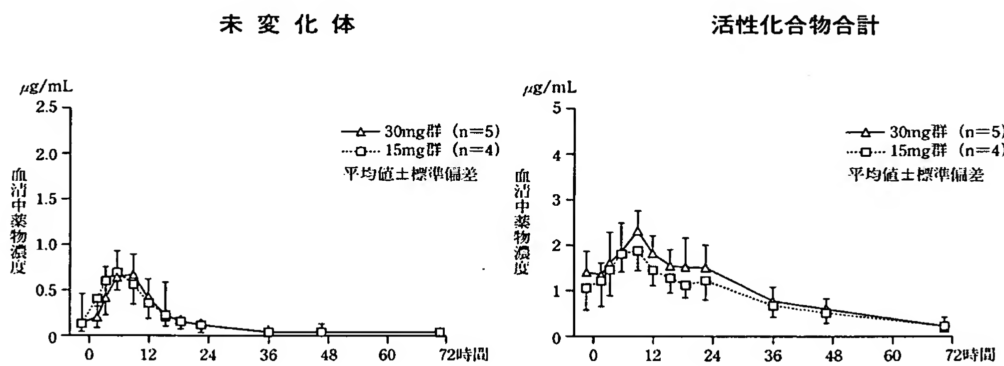
(3) 糖尿病患者での検討

食事療法のみの 2 型糖尿病患者を対象に、ピオグリタゾンとして 15mg あるいは 30mg を 1 日 1 回朝食後に 14 日間経口投与したとき、未変化体の C_{min} は投与 2〜3 日目に、活性化合物合計の C_{min} は投与 5 日目には定常状態に達した。また、定常状態（14 日目）における未変化体及び活性化合物合計の血清中濃度の推移は下記のとおりであった[15]。

■未変化体と活性化合物合計の血清中 C_{min} の推移



■定常状態における未変化体及び活性化合物合計の血清中濃度の推移



■定常状態における未変化体及び活性化合物合計のパラメータ

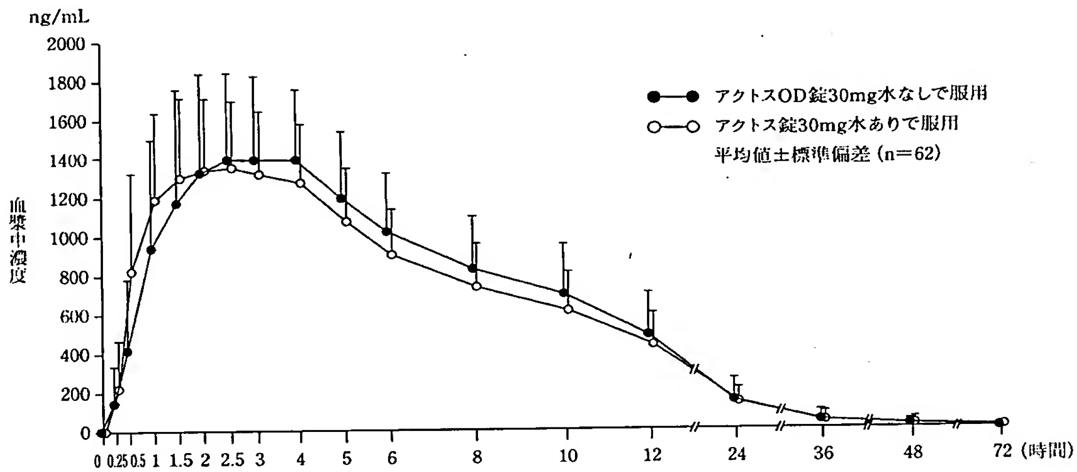
	投与量	例数	C_{max}（μg/mL）	C_{min}（μg/mL）	$AUC_{0\text{-}24h}$（μg・h/mL）	$t_{1/2}$（h）
未変化体	15mg	4	0.8±0.3	0.1±0.1	8.7±3.4	5.2± 1.4
	30mg	5	0.8±0.2	0.1±0.1	8.4±2.2	4.1± 1.2
活性化合物合計	15mg	4	1.9±0.4	1.1±0.5	34.5±9.2	19.3± 1.6
	30mg	5	2.4±0.4	1.4±0.4	41.6±9.7	23.6±10.1

平均値±標準偏差

(4) アクトス OD 錠とアクトス錠の生物学的同等性（健康成人）

健康成人 62 例を対象に、朝絶食時にクロスオーバー法にて、アクトス OD 錠 30 を水なしであるいはアクトス錠 30 を 200mL の水とともに単回経口投与したとき、未変化体の血漿中濃度は下記のとおりであり、生物学的に同等であると判断された。

■未変化体の血漿中濃度の推移



■未変化体及び活性化合物のパラメータ

		C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}72}$ (ng·h/mL)	$t_{1/2}$ (h)
未変化体	アクトス OD 錠	1548.6±477.9	2.73±1.09	16842.9±6540.0	6.73±2.32
	アクトス錠	1468.7±380.4	2.11±1.04	15536.7±4889.1	6.79±2.38
M－Ⅱ	アクトス OD 錠	40.5±13.7	8.28±2.96 1)	666.8±392.0	21.39±23.07 3)
	アクトス錠	38.5±11.5	7.48±3.21 2)	619.8±325.2	18.83±11.94 4)
M－Ⅲ	アクトス OD 錠	271.8±77.8	16.74±6.30	11809.6±3372.0	26.20±5.30
	アクトス錠	251.6±66.4	15.65±6.39	11122.3±3002.3	26.94±6.63
M－Ⅳ	アクトス OD 錠	568.0±112.7	17.03±7.17	25103.8±5060.2	25.68±6.05
	アクトス錠	535.6±107.0	15.10±6.82	23676.3±4341.4	25.43±5.55

平均値±標準偏差、n=62、1)：n=61、2)：n=60、3)：n=47、4)：n=48

［生物学的同等性の確認方法］

両剤投与後の未変化体血漿中濃度の実測値に基づく $AUC_{0\text{-}72}$、C_{max} の自然対数変換後の平均値の差の両側信頼区間（信頼係数：90%）が ln（0.8）～ln（1.25）の範囲にあるとき、両剤は生物学的に同等であると判断する。

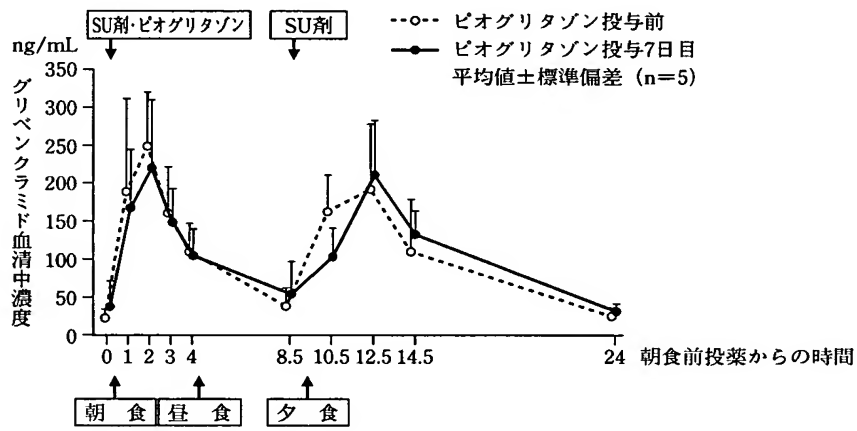
（承認時資料：2010 年 1 月）

(5) SU 剤併用時の血清中濃度

1) SU 剤の血清中濃度

グリベンクラミド 10mg/日（分 2）使用中の 2 型糖尿病患者 5 例を対象に、ピオグリタゾンとして 30mg を 7 日間併用投与し、ピオグリタゾン投与前及び 7 日目のグリベンクラミドの血清中濃度を測定したとき、ピオグリタゾン投与前後のグリベンクラミドの薬物動態に大きな変化は認められなかった。また、同時に検討されたグリクラジドでも同様な結果を示した[17]。

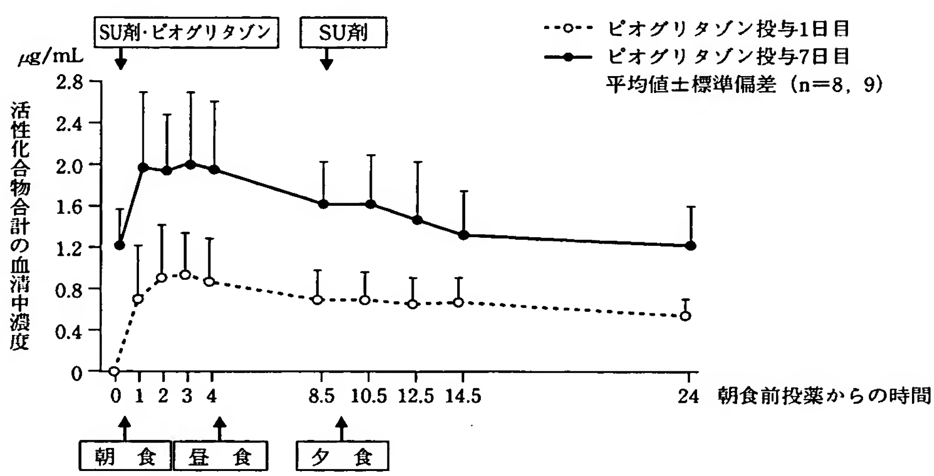
■グリベンクラミドの血清中濃度の推移



2) ピオグリタゾンの血清中濃度

グリベンクラミド 5～10mg/日（分 2）又はグリクラジド 160mg/日（分 2）使用中の 2 型糖尿病患者 9 例を対象に、ピオグリタゾンとして 30mg を 7 日間併用投与し、ピオグリタゾン投与の 1 日目と 7 日目の血清中濃度を測定したとき、活性化合物合計の投与 7 日目の薬物動態は、食事療法のみの 2 型糖尿病患者の薬物動態（39 頁参照）と近似していた[17]。

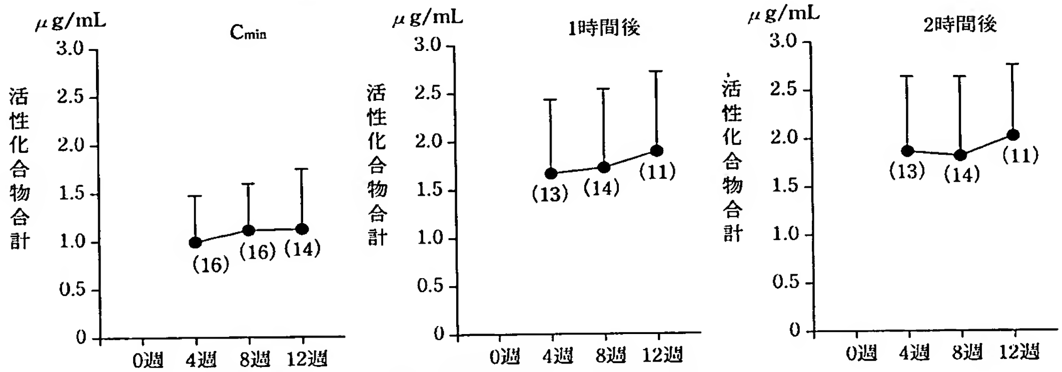
■ピオグリタゾンの血清中濃度の推移



(6) α-グルコシダーゼ阻害剤併用時のピオグリタゾンの血清中濃度

ボグリボース 0.6〜0.9mg/日（分 3）使用中の 2 型糖尿病患者 7 例及びボグリボース 0.6〜0.9mg/日（分 3）と SU 剤併用中の 2 型糖尿病患者 10 例を対象に、ピオグリタゾンとして 30mg を 12 週間併用投与して、ピオグリタゾンの血清中濃度を測定したとき、活性化合物合計の血清中 C_{min}、投与 1 時間後及び 2 時間後の濃度は、食事療法のみ及び SU 剤使用中の 2 型糖尿病患者の活性化合物合計の血清中濃度（39、41 頁参照）と近似していた[18]。

■活性化合物合計の血清中濃度の推移

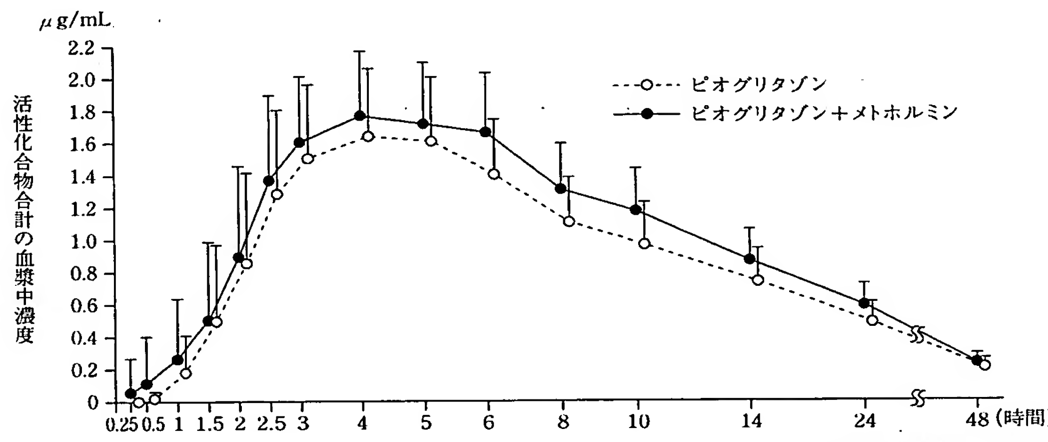


平均値±標準偏差，（ ）内は例数

(7) ビグアナイド系薬剤併用時のピオグリタゾンの血漿中濃度

健康成人男子 14 例を対象に、ピオグリタゾンとして 30mg を単回投与後、休薬期間をおいてメトホルミン塩酸塩 750mg/日（分 3）を 7 日間反復投与の 5 日目に、ピオグリタゾン 30mg を単回併用投与したとき、ピオグリタゾン単独投与時とメトホルミン併用投与時の活性化合物合計の血漿中濃度は近似していた。

■活性化合物合計の血漿中濃度の推移



平均値±標準偏差（n=14）

（承認時資料：2008 年 12 月）

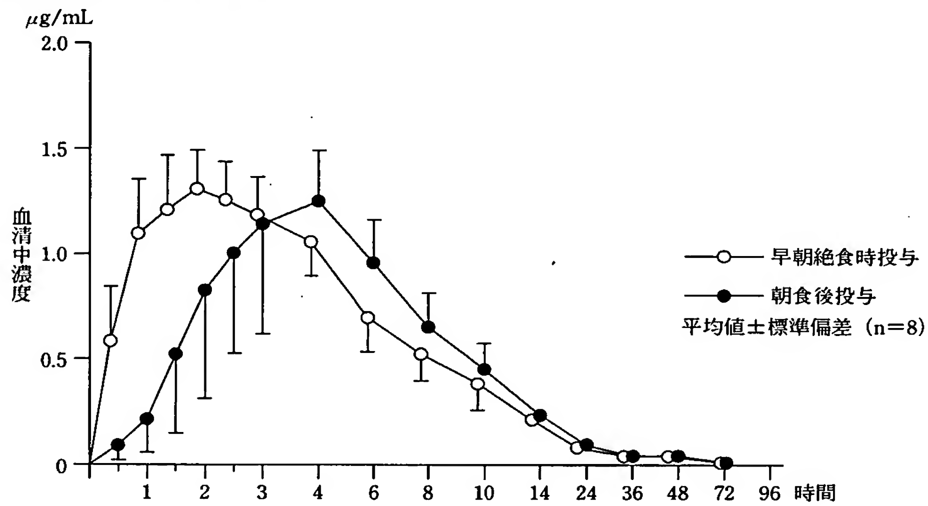
1−4　中毒域

該当資料なし

1−5　食事・併用薬の影響

健康成人 8 例を対象に、ピオグリタゾンとして 30mg を早朝絶食時あるいは朝食 30 分後に経口投与したとき、食後投与の場合は絶食時投与より未変化体の T_{max} の延長がみられたが、C_{max} 及び AUC に差異は認められなかった[1]。

■未変化体の血清中濃度の推移



■未変化体のパラメータ

投与条件	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0\text{-}336h}$ (μg・h/mL)	$t_{1/2}$ (h) α	$t_{1/2}$ (h) β
早朝絶食時	1.4±0.2	1.8±0.4	11.6±2.2	5.4±1.7	
				3.4±1.3[1]	8.7±2.1[1]
朝　食　後	1.4±0.3	3.7±1.1	11.2±2.5	4.0±0.8	

平均値±標準偏差（n=8）

1−6　母集団（ポピュレーション）解析により判明した薬物体内動態変動要因

該当資料なし

2. 薬物速度論的パラメータ

2−1 コンパートメントモデル

1-コンパートメントモデルで解析した。

2−2 吸収速度定数

該当資料なし

2−3 バイオアベイラビリティ

（参考）［マウス、ラット、イヌ、サル］

未変化体のバイオアベイラビリティはマウス、ラット、イヌ、サルでそれぞれ 81%、85%、94%、81%であった[19]。

2−4 消失速度定数

健康成人 62 例を対象に、朝絶食時にクロスオーバー法にて、アクトス OD 錠 30 を水なしであるいはアクトス錠 30 を 200mL の水とともに単回経口投与したとき、未変化体の消失速度定数はアクトス OD 錠、アクトス錠で 0.1108±0.02746h^{-1}、0.1122±0.02954h^{-1} であった（平均値±標準偏差）。

（承認時資料：2010 年 1 月）

2−5 クリアランス

健康成人 62 例を対象に、朝絶食時にクロスオーバー法にて、アクトス OD 錠 30 を水なしであるいはアクトス錠 30 を 200mL の水とともに単回経口投与したとき、未変化体のみかけのクリアランスはアクトス OD 錠、アクトス錠で 2.12±0.747L/h、2.00±0.688L/h であった（平均値±標準偏差）。

（承認時資料：2010 年 1 月）

2−6 分布容積

（参考）［海外データ］

タイ人の健康成人男子 24 例にピオグリタゾンとして 30mg を単回投与したとき、未変化体の分布容積は 30.19±13.06L であった（平均値±標準偏差）[20]。

2−7 血漿蛋白結合率

（参考）［*in vitro*、マウス、ラット、イヌ、サル］

［^{14}C］ピオグリタゾン塩酸塩（0.05、0.5、5μg/mL）を *in vitro* で、マウス、ラット、イヌ、サルの血漿、ヒトの血清、4%ヒト血清アルブミン溶液に添加したときの蛋白結合率は、いずれも 98%以上であった。

［^{14}C］ピオグリタゾン塩酸塩をマウス、ラット、イヌ、サルに経口投与したときの血漿タンパク質との結合率は、マウスで 0.5、1、6 時間後に 98%以上、ラットで 2、6、10 時間後に 99%以上、イヌで 0.5、2、6 時間後に 95～98%、サルでは 0.5、4、24 時間後に 98～99%であった[19]。

3. 吸　収

（参考）［マウス、ラット、イヌ、サル］

◇吸収部位

ラットの胃幽門部、小腸上部、小腸中央部、小腸下部、大腸の両端にループ（各 6cm）を形成し、各ループ内に［^{14}C］ピオグリタゾン塩酸塩を投与し、^{14}C の血漿中濃度から吸収部位を検討した。AUC_{0-4} はそれぞれ 0.54、1.00、0.95、0.98、0.47μg·h/mL であり、ピオグリタゾン塩酸塩は消化管全域から吸収された[19]。

◇吸収経路

［^{14}C］ピオグリタゾン塩酸塩を空腸ループ形成ラットにループ内に投与すると、2 時間で投与した ^{14}C の 53.7%が門脈経由で吸収され、残りは腸管壁と空腸ループ内容物から回収された。また、門脈血中の大部分（86%）は未変化体であり、吸収過程において一部は代謝されるが、主として未変化体で吸収された。一方、胸管ろう形成ラットに経口投与したときの。胸管リンパ液中への ^{14}C の回収は 24 時間で投与量の 4.5%であり、ラットに経口投与したピオグリタゾン塩酸塩は消化管から門脈を介して大部分が未変化体で吸収された[19]。

◇吸収率

［^{14}C］ピオグリタゾン塩酸塩を経口あるいは静脈内投与したときの ^{14}C の AUC 比を用いて計算した吸収率は、マウス、ラット、イヌ、サルでそれぞれ 88%、96%、95%、90%であった[19]。

4. 分　布

4−1　血液−脳関門通過性

（参考）［ラット］

ラットでは通過しにくい[19]。濃度はⅦ−4−5の項参照

4−2　血液−胎盤関門通過性

（参考）［ラット］

［^{14}C］ピオグリタゾン塩酸塩 0.5mg/kg を妊娠 20 日目のラットに経口投与すると、^{14}C 濃度は母体血漿＞胎児血漿＞胎盤＞胎児組織＞羊水であった。いずれの組織においても ^{14}C 濃度は母体血漿中濃度の減少に伴い低下した。胎児血漿中には未変化体のほか代謝物も移行し、組成は母体血漿とほぼ同じであった[19]。

■胎児への移行性

試　料	化合物	濃度（μg/mL or g）			
		2 時間	6 時間	10 時間	24 時間
母体血漿	総 ^{14}C	0.505±0.049	0.665±0.139	0.568±0.142	0.153±0.120
	未変化体	0.366±0.034	0.347±0.136	0.205±0.070	0.015±0.023
	M−Ⅱ	0.009±0.004	0.023±0.014	0.019±0.005	0.011±0.013
	M−Ⅲ	0.018±0.004	0.053±0.005	0.073±0.011	0.030±0.011
	M−Ⅳ	0.046±0.010	0.131±0.007	0.176±0.038	0.076±0.049
	M−Ⅴ	0.016±0.003	0.035±0.005	0.035±0.025	0.005±0.007
	その他	0.050±0.006	0.077±0.007	0.059±0.019	0.016±0.016
胎　盤	総 ^{14}C	0.194±0.014	0.311±0.123	0.252±0.071	0.116±0.091
羊　水	総 ^{14}C	0.073±0.013	0.088±0.025	0.095±0.028	0.099±0.048
胎児血漿	総 ^{14}C	0.244±0.025	0.396±0.218	0.306±0.095	0.109±0.092
	未変化体	0.189±0.020	0.236±0.153	0.118±0.055	0.010±0.015
	M−Ⅱ	0.003±0.002	0.010±0.010	0.007±0.001	0.006±0.009
	M−Ⅲ	0.003±0.001	0.014±0.007	0.014±0.003	0.008±0.003
	M−Ⅳ	0.021±0.002	0.075±0.027	0.103±0.027	0.052±0.034
	M−Ⅴ	0.004±0.002	0.013±0.007	0.016±0.009	0.014±0.016
	その他	0.024±0.004	0.047±0.016	0.048±0.004	0.019±0.015
胎児組織	総 ^{14}C	0.130±0.003	0.191±0.087	0.161±0.046	0.075±0.049

平均値±標準偏差、n=3

4−3 乳汁への移行性

（参考）［ラット］

[^{14}C] ピオグリタゾン塩酸塩 0.5mg/kg を出産後 14 日目のラットに経口投与すると、^{14}C は乳汁、乳腺中に移行した。その濃度は血漿中濃度より低く、^{14}C の組成は血漿と類似していた[19)]。

■乳汁、乳腺中への移行性

試料	化合物	濃度（μg/mL or g）			
		2 時間	6 時間	10 時間	24 時間
母体血漿	総 ^{14}C	0.786±0.026	0.425±0.030	0.227±0.033	0.032±0.022
	未変化体	0.602±0.003	0.195±0.046	0.049±0.021	<0.001
	M−Ⅰ	0.002±0.000	0.002±0.000	0.002±0.000	<0.001
	M−Ⅱ	0.012±0.009	0.012±0.009	0.006±0.003	0.001±0.001
	M−Ⅲ	0.020±0.002	0.040±0.011	0.032±0.009	0.005±0.005
	M−Ⅳ	0.066±0.012	0.097±0.013	0.090±0.023	0.018±0.015
	M−Ⅴ	0.020±0.004	0.016±0.004	0.014±0.002	<0.001
	M−Ⅵ	0.001±0.001	0.003±0.001	0.002±0.001	<0.001
	その他	0.063±0.008	0.060±0.004	0.031±0.004	0.008±0.003
乳汁	総 ^{14}C	0.173±0.032	0.176±0.016	0.135±0.016	0.029±0.009
	未変化体	0.102±0.020	0.030±0.009	0.009±0.004	<0.001
	M−Ⅰ	<0.001	<0.001	<0.001	<0.001
	M−Ⅱ	0.002±0.002	0.001±0.001	<0.001	<0.001
	M−Ⅲ	0.001±0.001	0.003±0.002	0.003±0.001	<0.001
	M−Ⅳ	0.030±0.003	0.041±0.007	0.048±0.008	0.011±0.009
	M−Ⅴ	0.009±0.003	0.012±0.003	0.009±0.002	<0.001
	M−Ⅵ	0.001±0.001	0.008±0.001	0.004±0.002	<0.001
	その他	0.029±0.006	0.082±0.004	0.062±0.015	0.018±0.004
乳腺	総 ^{14}C	0.258±0.036	0.166±0.016	0.110±0.009	0.018±0.009
	未変化体	0.164±0.024	0.047±0.015	0.014±0.005	<0.001
	M−Ⅰ	0.001±0.000	<0.001	<0.001	<0.001
	M−Ⅱ	0.003±0.003	0.002±0.002	0.001±0.001	<0.001
	M−Ⅲ	0.001±0.001	0.001±0.001	0.002±0.000	<0.001
	M−Ⅳ	0.035±0.006	0.049±0.004	0.052±0.013	0.009±0.008
	M−Ⅴ	0.007±0.002	0.007±0.001	0.006±0.001	<0.001
	M−Ⅵ	0.001±0.001	0.002±0.001	0.001±0.001	<0.001
	その他	0.046±0.005	0.057±0.003	0.033±0.005	0.010±0.003

平均値±標準偏差、n=3

4−4 髄液への移行性

該当資料なし

4—5　その他の組織への移行性

（参考）［ラット］

［^{14}C］ピオグリタゾン塩酸塩 0.5mg/kg をラットに経口投与すると、^{14}C は各組織に広く分布し、その濃度は胃壁を除く多くの組織で投与後 6 時間でピークとなった。^{14}C 濃度は肝臓以外の組織では血漿中濃度より低かった。投与後 6 時間における ^{14}C 濃度は肝臓で最も高く、次いで血漿、腎臓、ハーダー腺、副腎の順であり、脳、眼球で最も低かった[19)]。

■各組織への移行性

組織	^{14}C 濃度（μg/mL or g）					
	30 分	2 時間	6 時間	10 時間	24 時間	72 時間
血漿	0.28±0.03	0.87±0.04	0.97±0.03	0.52±0.16	0.06±0.01	＜0.01
脳	0.03±0.00	0.08±0.00	0.08±0.01	0.03±0.01	＜0.01	＜0.01
脊髄	0.03±0.00	0.09±0.01	0.09±0.01	0.04±0.01	＜0.01	＜0.01
下垂体	0.09±0.01	0.29±0.03	0.34±0.01	0.19±0.05	0.02±0.01	＜0.01
眼球	0.02±0.00	0.05±0.01	0.07±0.01	0.04±0.01	0.01±0.00	＜0.01
ハーダー腺	0.17±0.02	0.60±0.06	0.64±0.07	0.32±0.08	0.06±0.00	0.01±0.00
顎下腺	0.09±0.01	0.26±0.02	0.27±0.01	0.14±0.04	0.02±0.00	＜0.01
甲状腺	0.07±0.01	0.24±0.01	0.26±0.01	0.14±0.04	0.03±0.00	0.01±0.00
胸腺	0.04±0.00	0.12±0.00	0.14±0.00	0.08±0.02	0.01±0.00	＜0.01
心臓	0.11±0.01	0.30±0.02	0.34±0.02	0.17±0.05	0.02±0.00	＜0.01
肺	0.10±0.02	0.25±0.03	0.30±0.03	0.16±0.03	0.02±0.00	＜0.01
肝臓	0.47±0.05	1.28±0.05	1.60±0.15	1.10±0.27	0.13±0.02	0.02±0.00
脾臓	0.05±0.01	0.15±0.00	0.17±0.01	0.09±0.03	0.01±0.00	＜0.01
膵臓	0.07±0.01	0.20±0.02	0.22±0.02	0.11±0.03	0.01±0.00	＜0.01
副腎	0.14±0.02	0.39±0.02	0.42±0.02	0.22±0.07	0.04±0.00	0.01±0.00
腎臓	0.17±0.02	0.49±0.03	0.79±0.03	0.48±0.16	0.08±0.01	0.01±0.00
精巣	0.03±0.00	0.16±0.01	0.19±0.02	0.11±0.03	0.01±0.00	＜0.01
骨格筋	0.03±0.00	0.08±0.00	0.10±0.01	0.05±0.02	0.01±0.00	＜0.01
皮膚	0.05±0.00	0.18±0.01	0.21±0.03	0.12±0.03	0.02±0.00	＜0.01
白色脂肪	0.04±0.00	0.13±0.00	0.13±0.01	0.08±0.03	0.01±0.01	0.01±0.00
褐色脂肪	0.09±0.01	0.32±0.07	0.33±0.01	0.20±0.05	0.09±0.02	0.03±0.01
骨髄	0.05±0.01	0.16±0.01	0.19±0.01	0.10±0.03	0.02±0.00	＜0.01
胃壁	0.90±0.16	0.54±0.04	0.40±0.07	0.16±0.06	0.02±0.01	＜0.01
腸壁	0.12±0.04	0.25±0.01	0.35±0.03	0.30±0.10	0.04±0.01	＜0.01

平均値±標準偏差、n=3

5. 代　謝

5—1　代謝部位及び代謝経路

◇代謝部位

（参考）［*in vitro*］

ラットの脳、心臓、肺、肝臓、腎臓、十二指腸の切片と血液を用いた *in vitro* での試験の結果、ピオグリタゾンは肝臓で最も早く代謝され、次いで腎臓で代謝され、血液、心臓ではほとんど代謝されなかった。

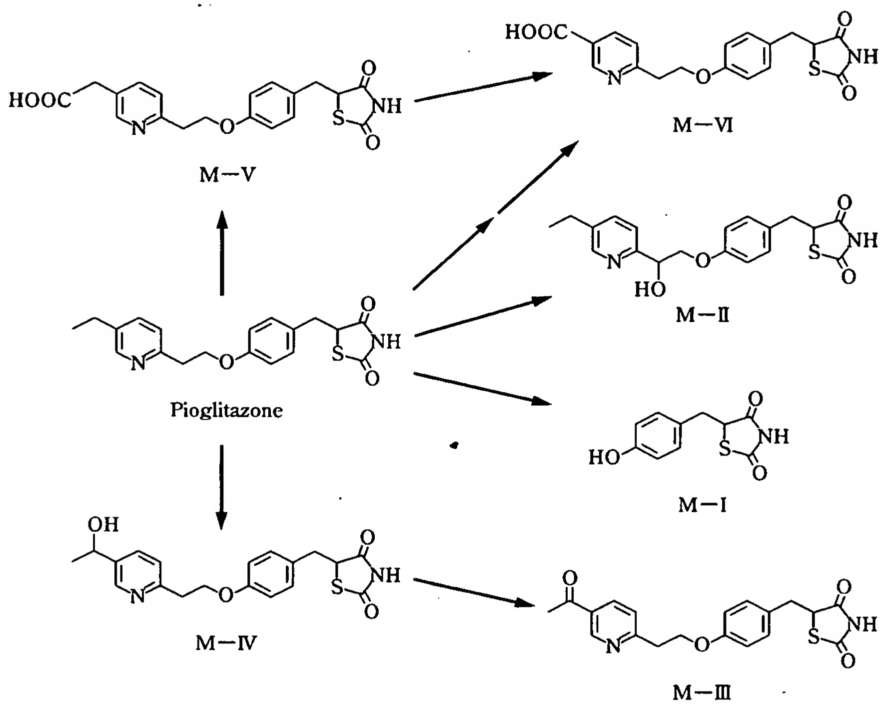
（承認時資料：1999 年 9 月）

◇代謝経路

（参考）［ラット、イヌ］

［^{14}C］ピオグリタゾン塩酸塩を投与したラット、イヌの体液、組織、排泄物中の代謝物を検索、同定し、下記の代謝経路を推定した。ピオグリタゾンは体内でアリールアルキルエーテルの開裂（M－Ⅰ）、メチレン部分の水酸化（M－Ⅱ、M－Ⅳ）、M－Ⅳの酸化（M－Ⅲ）、エチル基の酸化（M－Ⅴ）と末端炭素の脱離（M－Ⅵ）によって代謝され、さらに、代謝物の一部は抱合体として存在する[21]。

■ラットとイヌにおける推定代謝経路



5－2　代謝に関与する酵素（CYP450 等）の分子種

（参考）［*in vitro*］

ヒトの血清中の主代謝物であるM－Ⅳへの代謝にはCYP1A1、1A2、2C8、2C9（Arg）、2C9（Cys）、2C19、2D、3A4が、M－Ⅱへの代謝にはCYP2C8、2C9（Cys）が関与している。

（承認時資料：1999年9月）

5－3　初回通過効果の有無及びその割合

（参考）［マウス、ラット、イヌ、サル］

［^{14}C］ピオグリタゾン塩酸塩を経口あるいは静脈内投与したときの、^{14}CのAUC比を用いて計算した吸収率は、マウス、ラット、イヌ、サルでそれぞれ88%、96%、95%、90%であった。また、未変化体のAUC比から求めたバイオアベイラビリティは、それぞれ81%、85%、94%、81%であった。したがって、ピオグリタゾン塩酸塩は吸収に際して、一部は初回通過効果を受けるが、その程度は小さいと考えられた[19]。

5−4 代謝物の活性の有無及び比率

（参考）［ラット］

M−Ⅱ、M−Ⅲ、M−Ⅳ は、Wistar fatty ラットの血糖低下作用において、未変化体の約 1/2 の活性を示す活性代謝物である。比率は Ⅶ−1−3 の項参照

（承認時資料：1999 年 9 月）

5−5 活性代謝物の速度論的パラメータ

Ⅶ−1−3 の項参照

6. 排　泄

6−1 排泄部位及び経路

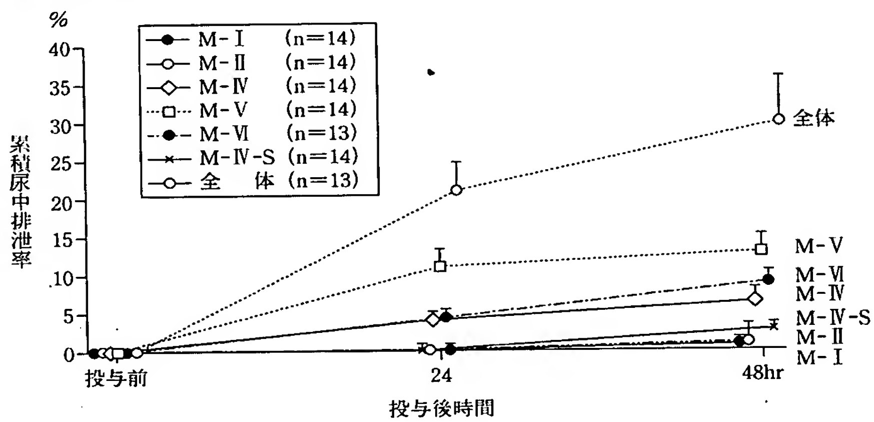
（参考）［マウス、ラット、イヌ、サル］

主排泄経路はマウス、ラット、イヌでは糞であるのに対し、サルでは尿であった[19]。

6−2 排 泄 率

健康成人を対象にピオグリタゾンとして 30mg を早朝空腹時に経口投与したとき、投与 48 時間までの非抱合体と抱合体を含む累積尿中排泄率は 29.6%であった。その主成分は M−Ⅴ（12.4%）、M−Ⅵ（7.8%）、M−Ⅳ（7.7%、M−Ⅳ−S を含む）であった[22]。

■累積尿中排泄率



（参考）［マウス、ラット、イヌ、サル］

［^{14}C］ピオグリタゾン塩酸塩をマウスに単回経口投与したときの排泄は 72 時間でほぼ終了し、投与した ^{14}C の 24%が尿に、75%が糞に排泄された。ラットに単回経口投与したときの排泄は 72 時間でほぼ終了し、投与した ^{14}C の 36%が尿に、63%が糞に排泄された。呼気への排泄は投与量の 1.2%であった。イヌにおける排泄は 96 時間でほぼ終了し、尿、糞への排泄率はそれぞれ投与量の 16%と 81%であった。サルでは 168 時間で尿、糞へそれぞれ投与量の 77%と 18%が排泄された。

［^{14}C］ピオグリタゾン塩酸塩を胆管ろう形成ラットの十二指腸内に投与すると、24 時間で投与した ^{14}C の 60%が胆汁に排泄された。この放射性胆汁を別の胆管ろう形成ラットの十二指腸内に投与すると、24 時間で胆汁と尿にそれぞれ投与した ^{14}C の 38%と 13%が排泄された。したがって、胆汁に排泄されたピオグリタゾンとその代謝物の一部は腸肝循環を行う[19]。

■経口投与時の排泄率

動物	時間 (h)	累積排泄率（投与量に対する%）			
		尿	糞	胆汁	総排泄率
マウス	8	9.6±3.9	ND	ND	ND
	24	21.9±5.6	66.5±10.5	ND	88.4±8.1
	48	23.9±5.9	74.9±7.7	ND	98.8±3.4
	72	24.0±5.9	75.4±7.6	ND	99.4±3.1
	96	24.1±5.9	75.5±7.6	ND	99.5±3.0
ラット	4	2.1±2.3	ND	ND	ND
	8	11.0±3.8	ND	ND	ND
	24	32.4±1.2	40.2±11.7	ND	72.6±12.8
	48	35.5±0.5	61.7±1.9	ND	97.2±1.6
	72	35.9±0.6	63.2±1.3	ND	99.1±0.8
	96	36.0±0.6	63.4±1.3	ND	99.4±0.8
ラット1)	4	0.5±0.1	ND	12.8±2.6	ND
	8	2.4±1.1	ND	31.9±5.2	ND
	24	13.7±3.9	15.9±2.12)	60.3±3.4	89.9±2.9
イヌ	4	0.8±1.4	ND	ND	ND
	8	1.4±1.3	ND	ND	ND
	24	11.7±0.3	25.4±25.6	ND	37.0±25.3
	48	15.1±1.0	60.4±26.5	ND	75.5±25.6
	72	16.0±1.5	79.9±1.7	ND	95.9±1.6
	96	16.3±1.5	80.8±1.5	ND	97.1±1.4
	120	16.4±1.5	81.1±1.4	ND	97.5±1.4
サル	4	8.4±2.9	ND	ND	ND
	8	24.6±3.5	ND	ND	ND
	24	59.8±2.6	1.3±2.1	ND	61.2±2.6
	48	69.7±1.4	5.2±3.3	ND	74.8±2.7
	72	73.9±1.5	10.7±5.3	ND	84.6±3.9
	96	75.9±2.1	13.7±6.1	ND	89.6±4.0
	120	76.8±2.4	16.1±5.2	ND	92.9±2.8
	144	77.2±2.4	17.1±4.7	ND	94.3±2.4
	168	77.4±2.5	17.6±4.4	ND	95.0±2.3

平均値±標準偏差、n=3
1) 胆管ろう形成ラット（十二指腸内投与）
2) 消化管内容物を含む

6−3　排泄速度

Ⅶ−6−2 の項参照

7. 透析等による除去率

該当資料なし

Ⅷ：安全性（使用上の注意等）に関する項目

1. 警告内容とその理由

該当しない

2. 禁忌内容とその理由

(1) 心不全の患者及び心不全の既往歴のある患者［動物試験において循環血漿量の増加に伴う代償性の変化と考えられる心重量の増加がみられており、また、臨床的にも心不全を増悪あるいは発症したとの報告がある。］
(2) 重症ケトーシス、糖尿病性昏睡又は前昏睡、1型糖尿病の患者［輸液、インスリンによる速やかな高血糖の是正が必須となる。］
(3) 重篤な肝機能障害のある患者［本剤は主に肝臓で代謝されるため、蓄積するおそれがある。］
(4) 重篤な腎機能障害のある患者
(5) 重症感染症、手術前後、重篤な外傷のある患者［インスリン注射による血糖管理が望まれるので本剤の投与は適さない。］
(6) 本剤の成分に対し過敏症の既往歴のある患者
(7) 妊婦又は妊娠している可能性のある婦人（「妊婦、産婦、授乳婦等への投与」の項参照）

3. 効能又は効果に関連する使用上の注意とその理由

糖尿病の診断が確立した患者に対してのみ適用を考慮すること。糖尿病以外にも耐糖能異常・尿糖陽性等、糖尿病類似の症状（腎性糖尿、老人性糖代謝異常、甲状腺機能異常等）を有する疾患があることに留意すること。

4. 用法及び用量に関連する使用上の注意とその理由

全製剤共通

(1) 浮腫が比較的女性に多く報告されているので、**女性に投与する場合は、浮腫の発現に留意し、1日1回15mgから投与を開始することが望ましい。**
(2) 1日1回30mgから45mgに増量した後に浮腫が発現した例が多くみられているので、**45mgに増量する場合には、浮腫の発現に留意すること。**
(3) **インスリンとの併用時**においては、浮腫が多く報告されていることから、**1日1回15mgから投与を開始すること。**本剤を増量する場合は浮腫及び心不全の症状・徴候を十分に観察しながら慎重に行うこと。ただし、1日量として30mgを超えないこと。
(4) 一般に**高齢者**では生理機能が低下しているので、**1日1回15mgから投与を開始することが望ましい。**

OD錠の場合

本剤は口腔内で崩壊するが、口腔粘膜からの吸収により効果発現を期待する製剤ではないため、唾液又は水で飲み込むこと。（「適用上の注意」の項参照）

5. 慎重投与内容とその理由

(1) 次に掲げる患者又は状態
1) 心不全発症のおそれのある心筋梗塞、狭心症、心筋症、高血圧性心疾患等の心疾患のある患者［循環血漿量の増加により心不全を発症させるおそれがある。］(「重要な基本的注意」、「重大な副作用」の項参照)
2) 肝又は腎機能障害（「禁忌」の項参照）
3) 脳下垂体機能不全又は副腎機能不全［低血糖を起こすおそれがある。］
4) 栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態［低血糖を起こすおそれがある。］
5) 激しい筋肉運動［低血糖を起こすおそれがある。］
6) 過度のアルコール摂取者［低血糖を起こすおそれがある。］
7) 高齢者（「高齢者への投与」の項参照）

(2) 他の糖尿病用薬を投与中の患者（「相互作用」、「重大な副作用」の項参照）

6. 重要な基本的注意とその理由及び処置方法

(1) 循環血漿量の増加によると考えられる浮腫が短期間に発現し、また心不全が増悪あるいは発症することがあるので、下記の点に留意すること。(「禁忌」、「慎重投与」の項参照)
1) 心不全の患者及び心不全の既往歴のある患者には投与しないこと。
2) 投与中は観察を十分に行い、浮腫、急激な体重増加、心不全症状等がみられた場合には投与中止、ループ利尿剤（フロセミド等）の投与等適切な処置を行うこと。
3) 服用中の浮腫、急激な体重増加、症状の変化に注意し、異常がみられた場合には直ちに本剤の服用を中止し、受診するよう患者を指導すること。

(2) 心電図異常や心胸比増大があらわれることがあるので、**定期的に心電図検査を行うなど十分に観察**し、異常が認められた場合には投与を一時中止するかあるいは減量するなど慎重に投与すること。(「その他の副作用」の項参照)

(3) 本剤は他の糖尿病用薬と併用した場合に低血糖症状を起こすことがあるので、これらの薬剤との併用時には患者に対し低血糖症状及びその対処方法について十分説明し、注意を喚起すること。(「相互作用」、「重大な副作用」の項参照)

(4) 本剤の適用はあらかじめ糖尿病治療の基本である食事療法、運動療法を十分に行ったうえで効果が不十分な場合に限り考慮すること。

(5) 本剤を使用する場合は、インスリン抵抗性が推定される患者に限定すること。インスリン抵抗性の目安は肥満度（Body Mass Index ＝ BMI kg/m^2）で24以上あるいはインスリン分泌状態が空腹時血中インスリン値で5μU/mL以上とする。

(6) 投与する場合には、血糖、尿糖を定期的に検査し、薬剤の効果を確かめ、3カ月間投与して効果が不十分な場合には、速やかに他の治療薬への切り替えを行うこと。

(7) 投与の継続中に、投与の必要がなくなる場合や、減量する必要がある場合があり、また、患者の不養生、感染症の合併等により効果がなくなったり、不十分となる場合があるので、食事摂取量、体重の推移、血糖値、感染症の有無等に留意のうえ、常に投与継続の可否、投与量、薬剤の選択等に注意すること。

(8) 急激な血糖下降に伴い、糖尿病性網膜症が悪化する例があることが知られており、本剤においても報告例があるので留意すること。
(9) α-グルコシダーゼ阻害剤と本剤1日45mgの併用における安全性は確立していない（使用経験はほとんどない）。
(10) α-グルコシダーゼ阻害剤、スルホニルウレア系薬剤及び本剤の3剤を併用投与する場合の安全性は確立していない（臨床試験成績より、副作用発現率が高くなる傾向が認められている）。
(11) ビグアナイド系薬剤と本剤1日45mgの併用における安全性は確立していない（使用経験はほとんどない）。

7. 相互作用

7－1 併用禁忌とその理由

該当しない

7－2 併用注意とその理由

薬剤名等	臨床症状·措置方法·機序等
糖尿病用薬 スルホニルウレア系薬剤 グリメピリド、グリベンクラミド、 グリクラジド、トルブタミド　等 スルホニルアミド系薬剤 グリブゾール ビグアナイド系薬剤 メトホルミン塩酸塩、ブホルミン塩酸塩 ナテグリニド、ミチグリニドカルシウム水和物 α-グルコシダーゼ阻害剤 ボグリボース、アカルボース　等 インスリン製剤	・左記の糖尿病用薬と併用した際に低血糖症状を発現するおそれがあるので、左記薬剤との併用時には、低用量から投与を開始するなど慎重に投与すること。 ・α-グルコシダーゼ阻害剤との併用により低血糖症状が認められた場合にはショ糖ではなくブドウ糖を投与すること。
糖尿病用薬及びその血糖降下作用を増強又は減弱する薬剤を併用している場合 ○糖尿病用薬の血糖降下作用を増強する薬剤 β-遮断剤、サリチル酸剤、 モノアミン酸化酵素阻害剤、 フィブラート系の高脂血症治療剤、 ワルファリン　等 ○糖尿病用薬の血糖降下作用を減弱する薬剤 アドレナリン、副腎皮質ホルモン、 甲状腺ホルモン　等	左記の併用に加え更に本剤を併用する場合には、糖尿病用薬の使用上の注意に記載の相互作用に留意するとともに、本剤のインスリン抵抗性改善作用が加わることによる影響に十分注意すること。
リファンピシン等のCYP2C8を誘導する薬剤	リファンピシンと併用するとピオグリタゾンのAUCが54％低下するとの報告があるので、リファンピシンと併用する場合は血糖管理状況を十分に観察し、必要な場合には本剤を増量すること。

8. 副作用

8－1 副作用の概要

承認時までのわが国での臨床試験では1日1回ピオグリタゾンとして15mg、30mg又は45mgが投与された1,368例中の364例（26.6％）に臨床検査値の異常を含む副作用が認められている。そのうち、浮腫は女性やインスリン併用時において多くみられており［本剤単独投与及びインスリンを除く他の糖尿病用薬との併用投与：男性3.9％（26/665例）、女性11.2％（72/643例）、インスリン併用投与：男性13.6％（3/22例）、女性28.9％（11/38例）］、また、糖尿病性合併症発症例での浮腫の発現頻度は非発症例に比べ高い傾向にある［糖尿病性網膜症合併例で10.4％（44/422例）、糖尿病性神経障害合併例で11.4％（39/342例）、糖尿病性腎症合併例で10.6％（30/282例）］。また、低血糖症状はインスリン併用時に多くみられている［本剤単独投与及びインスリンを除く他の糖尿病用薬との併用投与：0.7％（9/1,308例）、インスリン併用投与：33.3％（20/60例）］。
市販後の使用成績調査（再審査終了時点）では、3,421例中の556例（16.3％）に臨床検査値の異常を含む副作用が認められている。
以下の本剤での副作用は上記の調査あるいは自発報告等に基づくものである。

8－2 重大な副作用と初期症状

(1) **心不全が増悪あるいは発症**することがあるので、投与中は観察を十分に行い、浮腫、急激な体重増加、心不全症状･徴候（息切れ、動悸、心胸比増大、胸水等）がみられた場合には投与を中止し、ループ利尿剤等を投与するなど適切な処置を行うこと。**特に心不全発症のおそれのある心疾患の患者に投与する際やインスリンと併用する際には、心不全の徴候に注意すること。**（「慎重投与」、「重要な基本的注意」の項参照）

(2) 循環血漿量の増加によると考えられる**浮腫**（8.2％、112/1,368例）があらわれることがあるので、観察を十分に行い、浮腫が認められた場合には、減量あるいは中止するなど適切な処置を行うこと。これらの処置によっても症状が改善しない場合には、必要に応じてループ利尿剤（フロセミド等）の投与等を考慮すること。なお、**女性やインスリン併用時、糖尿病性合併症発症例において浮腫の発現が多くみられており、本剤を1日1回30mgから45mgに増量した後に浮腫が発現した例も多くみられている。**これらの症例にあっては浮腫の発現に特に留意すること。（**「用法･用量に関連する使用上の注意」の項参照**）

(3) AST（GOT）、ALT（GPT）、AL-P等の著しい上昇を伴う**肝機能障害、黄疸**（0.1％未満）があらわれることがあるので、基礎に肝機能障害を有するなど必要な場合には定期的に肝機能検査を実施し、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

(4) 他の糖尿病用薬との併用で、**低血糖症状**（0.1～5％未満）があらわれることがある。低血糖症状が認められた場合、本剤あるいは併用している糖尿病用薬を一時的に中止するかあるいは減量するなど慎重に投与すること。また、本剤の投与により低血糖症状が認められた場合には通常はショ糖を投与するが、**α-グルコシダーゼ阻害剤との併用によ**

り低血糖症状が認められた場合にはブドウ糖を投与すること。なお、低血糖症状はインスリン併用時に多くみられている。
(5) 筋肉痛、脱力感、CK（CPK）上昇、血中及び尿中ミオグロビン上昇を特徴とする**横紋筋融解症**（頻度不明）があらわれることがあるので、このような場合には投与を中止し、適切な処置を行うこと。
(6) 胃潰瘍が再燃した例が報告されている。

8－3　その他の副作用

	5％以上	0.1～5％未満	0.1％未満	頻度不明
1) 血　液[注1]		貧血、白血球減少、血小板減少		
2) 循環器		血圧上昇、心胸比増大[注2]、心電図異常[注2]、動悸、胸部圧迫感、顔面潮紅		
3) 過敏症[注3]		発疹、湿疹、瘙痒		
4) 消化器		悪心·嘔吐、胃部不快感、胸やけ、腹痛、腹部膨満感、下痢、便秘、食欲亢進、食欲不振		
5) 肝　臓[注4]		AST（GOT）、ALT（GPT）、AL-P、γ-GTPの上昇		
6) 精神神経系		めまい、ふらつき、頭痛、眠気、倦怠感、脱力感、しびれ		
7) その他	LDH及びCK(CPK)上昇[注5]	BUN及びカリウムの上昇、総蛋白及びカルシウムの低下、体重及び尿蛋白の増加、息切れ	関節痛、ふるえ、急激な血糖下降に伴う糖尿病性網膜症の悪化	骨折[注6]

注1) 血液検査を定期的（3カ月に1回程度）に行うこと。
注2)「重要な基本的注意（2）」の項参照
注3) このような場合には投与を中止すること。
注4) 発現頻度：AST（GOT）0.86％（11/1,272例）、ALT（GPT）0.94％（12/1,276例）、AL－P 0.47％（6/1,272例）、γ－GTP 0.95％（12/1,263例）
注5) LDH上昇（5.63％、71/1,261例）やCK（CPK）上昇（5.00％、61/1,221例）があらわれることがあるので、異常が認められた場合には、再検査を行うなど観察を十分に行うこと。
注6) 外国の臨床試験で、女性において骨折の発現頻度上昇が認められている。

■ 心不全及び浮腫について下記の点にご留意ください

［投与開始前のチェックポイント］

(1) 心不全を増悪あるいは発症したとの報告がありますので、心不全及び心不全の既往歴のある患者には投与しないでください。
循環血漿量の増加により心不全を発症させるおそれがありますので、心筋梗塞、狭心症、心筋症、高血圧性心疾患等の心疾患のある患者さんには、投与の必要性を十分に見極め、また、1日1回15mgから投与を開始するなど慎重に投与してください。
(2) 心不全を増悪あるいは発症したとの報告例には高齢者が多いこと、また、一般に

高齢者では生理機能が低下しているので、1日1回15mgから投与を開始するなど、浮腫、心不全の発現に留意し、経過を十分に観察しながら慎重に投与してください。

(3) 浮腫の発現には性差がみられることから、女性では1日1回15mgからの投与が望まれます。また、男性においても、慎重投与対象や浮腫、急激な体重増加、心不全症状等の発現が懸念される場合には1日1回15mgからの投与の開始を考慮するなど、慎重に投与してください。

(4) インスリンとの併用時には、浮腫が多く報告されていることから、1日1回15mgから投与を開始してください。本剤を増量する場合は浮腫及び心不全の症状・徴候を十分に観察しながら慎重に行い、1日量として30mgを超えないでください。

(5) 糖尿病性合併症がある場合は特に浮腫の発現に留意ください。
浮腫の発現頻度は、糖尿病性網膜症合併例で10.4％（44/422例）、糖尿病性神経障害合併例で11.4％（39/342例）、糖尿病性腎症合併例で10.6％（30/282例）であり、糖尿病性合併症発症例は非発症例に比べ高い傾向にあります。

[投与中のチェックポイント]

(1) 投与中は観察を十分に行い、浮腫、急激な体重増加、心不全症状・徴候（息切れ、動悸、心胸比増大、胸水等）がみられた場合には投与中止し、ループ利尿剤（フロセミド等）の投与等の処置を行ってください。
患者さんには、服用中の浮腫、急激な体重増加、症状の変化に注意させ、異常がみられた場合には直ちに本剤の服用を中止し、受診するように十分な指導を行ってください。
また、循環血漿量の増加による心臓への容量負荷の結果、心電図異常や心胸比増大があらわれることがありますので、定期的に心電図検査、胸部X線検査等を行うなど十分な観察を行ってください。
特に心不全発症リスクのある患者さんでは心エコー検査やBNPの測定等をご考慮ください。

[異常発現時の対策]

浮腫、急激な体重増加、心不全症状がみられた場合

①心不全症状・徴候（息切れ、動悸、心胸比増大、胸水等）もみられた場合には、本剤の投与を中止し、適切に治療を行うとともに、慎重に経過を観察してください。

②心不全の症状・徴候はみられず、心不全を否定することができた場合は、他要因の可能性、かつ利尿剤の併用や本剤の減量、他剤への変更等を考慮してください。

■ 肝機能障害について下記の点にご留意ください

[投与開始前のチェックポイント]

肝機能障害のある患者さんには慎重に投与してください。
また、重篤な肝機能障害のある患者さんには投与しないでください。

[投与中のチェックポイント]

基礎に肝機能障害を有するなど必要な場合には定期的に肝機能検査を実施してください。
検査結果は、できるだけ次回の受診を待たず、入手した時点で確認してください。

[異常発現時の対策]

異常が認められた場合には投与を中止するなど適切な処置をお願いいたします。

■ 低血糖について下記の点にご留意ください

［投与前のチェックポイント］

(1) 患者さん及び家族の方に低血糖症状とその対処方法について十分にご説明・ご指導ください。

(2) 重篤な肝機能障害、腎機能障害を合併した患者さんには投与しないでください。

(3) 次の患者さんには低血糖が発現しやすくなりますので慎重に投与してください

①他の糖尿病用薬（特にインスリン製剤）の使用

低血糖症状はインスリン併用時に多くみられている［本剤単独投与及びインスリンを除く他の糖尿病用薬との併用投与：0.7％（9/1,308例）、インスリン併用投与：33.3％（20/60例）］

②肝機能障害の合併

③腎機能障害の合併

④脳下垂体機能不全又は副腎機能不全の合併

⑤栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態

⑥激しい運動や食前・空腹時の運動

⑦過度のアルコール摂取

⑧下痢が続いたり、発熱しているなど体調が優れない場合（Sick Day）　等

［投与中のチェックポイント］

以下の症状の発現に留意するよう患者さんに指導ください。

①強い空腹感、②発汗、③手指がふるえる、④動悸がする、

⑤落ち着かずイライラする、⑥顔が蒼くなる、⑦頭痛、⑧吐き気、⑨目がかすむ、

⑩体がふらつく、⑪眠ってわからなくなる（昏睡）、⑫ひきつる（痙攣）　等

このような症状が認められた際に、下記のような処置をとるよう指導ください。

［異常発現時の対策］

低血糖が疑われる症状が発現した場合には、次のような処置をとるよう、患者本人及び家族の方をご指導ください。

(1) 経口摂取が可能な場合

①砂糖10g又は食事を摂取する。ただし、α-グルコシダーゼ阻害剤を服用している場合や服用の有無が不明な場合はブドウ糖10gを服用するか、ブドウ糖含有飲料を飲む。

②10分以内に症状が改善しない場合には電話連絡の上、医療機関を受診する。

(2) 経口摂取が不可能な場合（昏睡、意識障害等）

①患者の家族が医療機関へ速やかに連絡する。

②医療機関へ連絡後速やかに患者を受診させる。

8－4　項目別副作用発現頻度及び臨床検査値異常一覧

○臨床試験（初回承認時及びα－GI追加承認時）及び市販後調査の副作用

■副作用の発現状況

	臨床試験	市販後調査
調査症例数	1,225	3,421
副作用発現例数	311	556
副作用発現件数	542	947
副作用発現症例率(%)	25.4	16.3

■副作用の種類別発現頻度

副作用の種類	臨床試験	市販後調査
[感染症及び寄生虫症]	2 (0.16)	1 (0.03)
鼻咽頭炎	1 (0.08)	0
上気道感染	0	1 (0.03)
ヘルペスウイルス感染	1 (0.08)	0
[良性、悪性及び詳細不明の新生物]	1 (0.08)	1 (0.03)
結腸癌	1 (0.08)	0
肺の悪性新生物	0	1 (0.03)
[血液及びリンパ系障害]	17 (1.39)	3 (0.09)
貧　血	0	3 (0.09)
血小板減少症	[6/1,177] (0.51)	0
赤血球増加症	[1/1,177] (0.08)	0
白血球減少症	[12/1,177] (1.02)	0
[代謝及び栄養障害]	13 (1.06)	20 (0.58)
食欲不振	0	3 (0.09)
食欲亢進	5 (0.41)	0
肥　満	0	1 (0.03)
食欲減退	0	1 (0.03)
高コレステロール血症	0	1 (0.03)
低ナトリウム血症	0	2 (0.06)
多飲症	0	1 (0.03)
低血糖症	8 (0.65)	12 (0.35)
低蛋白血症	0	1 (0.03)
[精神障害]	0	1 (0.03)
落ち着きのなさ	0	1 (0.03)
易刺激性	0	1 (0.03)
人格変化	0	1 (0.03)
不眠症	0	1 (0.03)
[神経系障害]	10 (0.82)	30 (0.88)
脳梗塞	0	1 (0.03)
頭　痛	2 (0.16)	9 (0.26)
片麻痺	0	1 (0.03)
麻　痺	0	1 (0.03)
振　戦	0	1 (0.03)

副作用の種類	臨床試験	市販後調査
意識レベルの低下	1 (0.08)	0
浮動性めまい	5 (0.41)	14 (0.41)
体位性めまい	1 (0.08)	1 (0.03)
頭部不快感	0	2 (0.06)
感覚減退	1 (0.08)	3 (0.09)
味覚減退	0	1 (0.03)
錯感覚	1 (0.08)	0
傾　眠	2 (0.16)	3 (0.09)
[眼障害]	4 (0.33)	7 (0.20)
眼瞼浮腫	0	3 (0.09)
眼充血	0	1 (0.03)
結膜充血	0	1 (0.03)
眼の異常感	2 (0.16)	0
眼精疲労	0	1 (0.03)
網膜症	1 (0.08)	0
霧　視	1 (0.08)	1 (0.03)
[耳及び迷路障害]	0	2 (0.06)
回転性眩暈	0	1 (0.03)
耳痛	0	1 (0.03)
[心臓障害]	13 (1.06)	36 (1.05)
心房細動	0	1 (0.03)
頻　脈	1 (0.08)	0
心室性不整脈	0	1 (0.03)
心室性期外収縮	0	1 (0.03)
動悸	5 (0.41)	15 (0.44)
急性心筋梗塞	0	1 (0.03)
狭心症	0	2 (0.06)
心不全	0	7 (0.20)
急性心不全	0	1 (0.03)
うっ血性心不全	0	1 (0.03)
心拡大	[7/464] (1.51)	13 (0.38)
[血管障害]	2 (0.16)	1 (0.03)
ほてり	2 (0.16)	1 (0.03)

副作用の種類	臨床試験	市販後調査
[呼吸器、胸郭及び縦隔障害]	2 (0.16)	19 (0.56)
喘　息	0	1 (0.03)
肺うっ血	0	2 (0.06)
胸　水	0	5 (0.15)
咳　嗽	0	1 (0.03)
呼吸困難	2 (0.16)	13 (0.38)
労作性呼吸困難	0	3 (0.09)
咽喉頭疼痛	0	1 (0.03)
咽頭不快感	0	1 (0.03)
あくび	0	1 (0.03)
[胃腸障害]	27 (2.20)	21 (0.61)
胃腸出血	0	1 (0.03)
便　秘	5 (0.41)	2 (0.06)
下　痢	2 (0.16)	2 (0.06)
腹部不快感	2 (0.16)	0
腹部膨満	10 (0.82)	2 (0.06)
腹　痛	1 (0.08)	2 (0.06)
上腹部痛	0	3 (0.09)
消化不良	1 (0.08)	2 (0.06)
おくび	2 (0.16)	0
鼓　腸	2 (0.16)	0
悪　心	4 (0.33)	5 (0.15)
レッチング	2 (0.16)	0
胃不快感	4 (0.33)	1 (0.03)
嘔　吐	3 (0.24)	3 (0.09)
胃潰瘍	1 (0.08)	0
口唇びらん	0	1 (0.03)
舌　炎	1 (0.08)	1 (0.03)
排便回数増加	1 (0.08)	0
胃　炎	1 (0.08)	0
口内炎	1 (0.08)	0
[肝胆道系障害]	0	31 (0.91)
肝機能異常	0	26 (0.76)
肝障害	0	5 (0.15)
[皮膚及び皮下組織障害]	10 (0.82)	21 (0.61)
蕁麻疹	0	1 (0.03)
水疱性皮膚炎	0	1 (0.03)
薬　疹	0	1 (0.03)
湿　疹	1 (0.08)	2 (0.06)
紅　斑	1 (0.08)	2 (0.06)
光線過敏性反応	1 (0.08)	0
瘙痒症	2 (0.16)	12 (0.35)
発　疹	3 (0.24)	3 (0.09)
全身性皮疹	0	1 (0.03)
丘　疹	0	1 (0.03)
皮膚障害	0	1 (0.03)
顔面腫脹	0	1 (0.03)
全身性瘙痒症	0	2 (0.06)

副作用の種類	臨床試験	市販後調査
中毒性皮疹	0	1 (0.03)
無汗症	1 (0.08)	0
冷　汗	2 (0.16)	0
皮下出血	0	1 (0.03)
[筋骨格系及び結合組織障害]	3 (0.24)	7 (0.20)
関節痛	1 (0.08)	2 (0.06)
背部痛	1 (0.08)	3 (0.09)
四肢痛	0	1 (0.03)
肩部痛	0	1 (0.03)
筋骨格硬直	0	2 (0.06)
筋　痛	1 (0.08)	0
[腎及び尿路障害]	7 (0.57)	3 (0.09)
乏　尿	0	1 (0.03)
ビリルビン尿	[1/1,120] (0.09)	0
ケトン尿	[3/1,159] (0.26)	0
頻　尿	1 (0.08)	1 (0.03)
多　尿	1 (0.08)	1 (0.03)
血　尿	1 (0.08)	0
[生殖系及び乳房障害]	1 (0.08)	0
女性化乳房	1 (0.08)	0
[全身障害及び投与局所様態]	106 (8.65)	333 (9.73)
悪　寒	0	1 (0.03)
発　熱	0	1 (0.03)
無力症	1 (0.08)	4 (0.12)
胸部不快感	1 (0.08)	7 (0.20)
胸　痛	1 (0.08)	4 (0.12)
顔面浮腫	0	31 (0.91)
疲　労	6 (0.49)	1 (0.03)
異常感	18 (1.47)	10 (0.29)
全身性浮腫	0	5 (0.15)
飢　餓	4 (0.33)	3 (0.09)
倦怠感	1 (0.08)	13 (0.38)
浮　腫	78 (6.37)	159 (4.65)
末梢性浮腫	0	113 (3.30)
疼　痛	1 (0.08)	0
圧痕浮腫	0	1 (0.03)
口　渇	0	1 (0.03)
[臨床検査]	187 (15.27)	235 (6.87)
血圧上昇	[7/1,195] (0.59)	3 (0.09)
心電図異常	[10/502] (1.99)	0
心電図ST部分上昇	0	1 (0.03)
心拍数増加	0	1 (0.03)
心電図異常T波	0	1 (0.03)
心エコー像異常	[3/211] (1.42)	0
血中CK (CPK) 増加	[53/1,161] (4.57)	29 (0.85)
血中LDH増加	[60/1,201] (5.00)	58 (1.70)
CK (CPK) 減少	0	1 (0.03)
血中AL-P増加	[6/1,212] (0.50)	17 (0.50)

副作用の種類	臨床試験	市販後調査
ヘマトクリット減少	[12/1,178] (1.02)	1 (0.03)
ヘマトクリット増加	[4/1,178] (0.34)	0
ヘモグロビン減少	[1/1,178] (0.08)	2 (0.06)
ヘモグロビン増加	[1/1,178] (0.08)	0
平均赤血球ヘモグロビン減少	[14/1,178] (1.19)	0
血小板数減少	0	1 (0.03)
赤血球数減少	[18/1,177] (1.53)	2 (0.06)
白血球数減少	0	2 (0.06)
血小板数増加	[1/1,177] (0.08)	0
ALT (GPT) 増加	[11/1,216] (0.90)	50 (1.60)
AST (GOT) 減少	0	1 (0.03)
AST (GOT) 増加	[9/1,212] (0.74)	39 (1.14)
血中ビリルビン増加	[2/1,189] (0.17)	7 (0.20)
γ-GTP増加	[11/1,203] (0.91)	32 (0.94)
血中コレステロール増加	0	2 (0.06)
血中ブドウ糖減少	0	1 (0.03)
血中ブドウ糖増加	0	2 (0.06)
血中尿酸増加	[3/1,201] (0.25)	0
血中尿酸減少	[2/1,201] (0.17)	0
BNP上昇	0	2 (0.06)
尿中ケトン体陽性	0	1 (0.03)

副作用の種類	臨床試験	市販後調査
血中アルブミン減少	[5/1,187] (0.42)	0
総蛋白減少	[8/1,204] (0.66)	0
総蛋白増加	[1/1,204] (0.08)	0
血中クレアチニン減少	[1/1,214] (0.08)	0
血中クレアチニン増加	[1/1,214] (0.08)	0
BUN増加	[13/1,215] (1.07)	0
尿中蛋白陽性	[2/1,161] (0.17)	0
尿量減少	1 (0.08)	2 (0.06)
肺血管造影異常	0	1 (0.03)
胸部X線異常	0	1 (0.03)
血中カルシウム減少	[8/1,121] (0.71)	0
血中カルシウム増加	[1/1,121] (0.09)	0
血中クロール減少	[3/1,199] (0.25)	1 (0.03)
血中クロール増加	[1/1,199] (0.08)	0
血中カリウム減少	[1/1,178] (0.08)	0
血中カリウム増加	[11/1,178] (0.93)	1 (0.03)
血中ナトリウム減少	[1/1,200] (0.08)	0
血中ナトリウム増加	[1/1,200] (0.08)	0
血中リン増加	[3/1,090] (0.28)	0
体重減少	0	1 (0.03)
体重増加	7 (0.57)	82 (2.40)

(臨床試験：2002年6月承認時資料集計)
(市販後調査：2005年11月集計)

○ビグアナイド系薬剤追加承認時の副作用

83例中13例（15.7％）に副作用が認められた。その副作用は浮腫3件、末梢性浮腫、上腹部痛及びBNP上昇が各2件、低血糖症、浮動性めまい、下腹部痛、下痢、消化不良、嘔吐及び肝機能障害が各1件であった。

(2008年12月承認時資料集計)

○インスリン製剤追加承認時の副作用

60例中40例（66.7％）に副作用が認められた。その副作用は低血糖症20件、末梢性浮腫及び血中LDH増加各11件、血中CK（CPK）増加8件、赤血球数減少7件、体重増加4件、腹痛、浮腫、ヘマトクリット減少、ヘモグロビン減少及び総蛋白減少各3件、心拡大、腹部膨満、下痢、異常感、発熱及びAST（GOT）増加各2件、扁桃炎、抑うつ症状、頭痛、感覚鈍麻、不整脈、咳嗽、異常便、消化不良、嘔吐、湿疹、胸部不快感、疲労、倦怠感、ALT（GPT）増加、血中アルブミン減少、血中ナトリウム増加、血中尿素増加、血中尿酸減少、血中尿酸増加、γ-GTP増加、尿中血陽性、血小板数減少、白血球数減少及び尿中蛋白陽性各1件であった。

(2009年3月承認時資料集計)

なお、重大な副作用として**心不全の増悪あるいは発症、浮腫、肝機能障害、黄疸、低血糖症状、横紋筋融解症、胃潰瘍の再燃**が認められている。

8－5　基礎疾患、合併症、重症度及び手術の有無等背景別の副作用発現頻度

該当資料なし

8－6　薬物アレルギーに対する注意及び試験法

○禁忌

本剤の成分に対し過敏症の既往歴のある患者

○その他の副作用

発疹、湿疹、瘙痒等があらわれた場合には投与を中止すること。

9. 高齢者への投与

一般に高齢者では生理機能が低下しているので、1日1回15mgから投与を開始するなど、副作用発現に留意し、経過を十分に観察しながら慎重に投与すること。

10. 妊婦、産婦、授乳婦等への投与

(1) 妊婦又は妊娠している可能性のある婦人には投与しないこと。［妊娠中の投与に関する安全性は確立していない。また、ラット器官形成期投与試験では、40mg/kg以上の群で胚・胎児死亡率の高値、出生児の生存率の低値が、ウサギ器官形成期投与試験では、160mg/kg群で親動物の死亡又は流産がそれぞれ1例、胚・胎児死亡率の高値がみられている。］

(2) 授乳中の婦人に投与することは避け、やむを得ず投与する場合は授乳を中止させること。［ラットで乳汁中への以降が報告されている。］[19)]

11. 小児等への投与

小児等に対する安全性は確立していない（使用経験がない）。

12. 臨床検査結果に及ぼす影響

該当しない

13. 過量投与

該当しない

14. 適用上の注意

全製剤共通

薬剤交付時：PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。［PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することが報告されている。］

OD錠の場合

服　用　時：本剤は舌の上にのせ唾液を浸潤させ舌で軽くつぶし、崩壊後唾液のみで服用可能である。また、水で服用することもできる。

15. その他の注意

(1) ラット及びマウスに24カ月間強制経口投与した試験では、ラット雄の3.6mg/kg/日以上の群に膀胱腫瘍がみられた。

(2) 家族性大腸腺腫症（familial adenomatous polyposis ： FAD）のモデル動物であるMinマウスに類薬（トログリタゾン及びロシグリタゾン）を経口投与したところ、結腸腫瘍の数及び大きさを増大させたとの報告がある[23,24]。

(3) 本剤等のチアゾリジン系薬剤を投与したところ（糖尿病性）黄斑浮腫が発生または増悪したとの報告がある。視力低下があらわれた場合には黄斑浮腫の可能性を考慮すること。

16. その 他

該当しない

Ⅸ：非臨床試験に関する項目

1. 薬理試験

1−1 薬効薬理試験（「Ⅵ：薬効薬理に関する項目」参照）

1−2 副次的薬理試験

該当資料なし

1−3 安全性薬理試験

ピオグリタゾン塩酸塩の一般薬理作用を各種動物を用いて検討した。

ピオグリタゾン塩酸塩の300mg/kg（経口投与）でマウスの一般症状観察において軽度な鎮静が認められたが、中枢神経系の各試験においては作用を示さなかった。循環器系においては、無麻酔イヌ（30mg/kg）の経口投与及び無麻酔ラット（300mg/kg）の経口投与でも全身血圧及び心拍数に作用を示さなかった。さらに、麻酔イヌ（10mg/kg）の十二指腸内投与でも血圧、心拍数及び末梢血流量に対して作用を示さなかった。また、同用量の麻酔ネコの自律神経機能に対しても作用を示さなかった。モルモットの摘出回腸のアゴニスト（アセチルコリン、ヒスタミン、バリウム）の濃度−反応曲線に対しては10^{-4}mol/Lの高濃度でいずれのアゴニストに対しても軽度な抑制作用を示した。ラットの腎機能及び消化器系に対しては作用を示さなかった。摘出平滑筋標本に対しては10^{-4}mol/Lの高濃度でウサギ回腸の自動運動を軽度抑制した。

以上の成績より、ピオグリタゾン塩酸塩は単回投与の高用量でも中枢神経系、循環器系、自律神経系、腎機能、消化器系及び平滑筋機能に対して危惧すべき急性の薬理活性を示さなかった[25]。

また、マウスの急性毒性試験で本体に比較して、ほぼ同等の毒性を示したM−Ⅲ及びM−Ⅳについても一般薬理作用を一部検討した。M−Ⅲは30mg/kg（腹腔内）でマウスの最大電撃痙攣、ラットの胃排出能及び腸管内輸送能を抑制した。M−Ⅳは10及び30mg/kg（腹腔内）でマウスの最大電撃痙攣の抑制、マウスのペントバルビタール睡眠時間の延長及びラットの胃排出能の抑制を示した。

（武田薬品・研究所）

1−4 その他の薬理試験

該当資料なし

2. 毒性試験

2−1 単回投与毒性試験

LD_{50}、mg/kg、ピオグリタゾンとして

投与経路 ＼ 動物種	マウス		ラット	
	♂	♀	♂	♀
経口	＞1814	＞1814	＞1814	＞1814

（武田薬品・研究所）

2－2　反復投与毒性試験

動 物 種	投与期間	投与経路	投与量（mg/kg/日）	無毒性量（mg/kg/日）
ラット	13週間	経　口	3.6、14.5、57.1、145.1	3.6
イ　ヌ	13週間	経　口	1、3、10	3
サ　ル	13週間	経　口	8、32、125	＜8
ラット	26週間	経　口	9.1、27.2、90.7	27.2
イ　ヌ	26週間	経　口	0.91、2.72、9.1	2.72
ラット	52週間	経　口	3.6、14.5、57.1、145.1	＜3.6
ラット	52週間	経　口	0.23、0.91、3.63	0.91
イ　ヌ	52週間	経　口	1、3、10	1（♂）、3（♀）
サ　ル	52週間	経　口	1、2、8、32	＞32

投与量及び無毒性量はピオグリタゾンとして表示

ラットの13週間試験の14.5mg/kg以上、26週試験の90.7mg/kg及び52週試験の3.6mg/kg以上で、また、イヌの13週試験の10mg/kg、26週試験の9.1mg/kg、52週試験の雄の3mg/kg以上及び雌の10mg/kgで心重量の高値及び軽度な貧血がみられた。サルの13週試験では8mg/kg以上で心重量の高値傾向がみられたが、52週試験では32mg/kgにおいても心重量の変化はみられなかった。ラットの高用量を用いた13週試験では、高度の心肥大の持続による二次的変化と考えられる胸水貯留、両側性心房肥大及び肺重量の増加を主徴とする心機能障害の徴候及び単核細胞浸潤、線維増生及び心筋の巣状壊死が雄14.5mg/kg以上及び雌57.1mg/kg以上で認められた。これら反復投与毒性試験の成績から本薬の主要な標的器官は心臓と考えられた。

インスリンの生理作用の一つに腎尿細管でのナトリウムの再吸収を促進させる作用、すなわち抗利尿作用が報告されている。ピオグリタゾン塩酸塩はインスリン感受性を増強させる作用を有するため、本薬が大量かつ長期間にわたって投与された場合には、インスリンの生理作用が過度に発現し、ナトリウムとともに再吸収された余剰な水は細胞内外に貯留されるか、循環血漿量あるいは血液量を増加させると考えられる。ラット、イヌ及びサルにおいて、本薬の投与により心重量の高値とともに循環血漿量あるいは血液量が増加した。

心重量の高値の成因については別途、心エコー等により詳細な解析を行った結果、循環血漿量の増加に起因する継続的な心臓への容量負荷によることが判明し、本薬による心肥大は適応あるいは代償性の変化と考えられた。また、貧血は循環血漿量の増加に起因した二次的な変化と考えられる。このほか、ラットでは脂肪組織の変化（脂肪細胞の肥大及び過形成）及び骨に対する影響（胸骨骨形成異常及び大腿骨、脛骨骨端線閉鎖）がみられたが、イヌ及びサルではこれらの変化はなかった。

（武田薬品・研究所）

2－3　生殖発生毒性試験

	動物種	投与期間・時期	投与量 (mg/kg/日)	無毒性量 (mg/kg/日)	
				親	胎児・新生児
Seg I	ラット	経口（♂交配前10週から剖検前日）（♀交配前2週から妊娠19日あるいは分娩後21～23日）	10、20、40	<10	<10
	ラット	経口（♂交配前10週から剖検前日）（♀交配前2週から妊娠19日あるいは分娩後21～23日）	0.3、1、3、10	3	10
Seg II	ラット	経口・12日（妊娠6～17日）	20、40、80	<20	<20
	ラット	経口・12日（妊娠6～17日）	1、3、10、20	3	10
	ウサギ	経口・13日（妊娠6～18日）	40、80、160	40	80
Seg III	ラット	経口・4週（妊娠15～分娩後21日）	10、20、40	<10	<10
	ラット	経口・4週（妊娠15～分娩後22日）	0.3、1、3、10	1	3

投与量及び無毒性量はピオグリタゾンとして表示

親動物の観察で、Seg Iのラット雄10mg/kgで摂餌量の増加を伴った体重増加の促進、雌で妊娠期に摂餌量の高値がみられたが、生殖機能には異常はなかった。Seg IIのラット10及び20mg/kgでは体重増加の抑制（妊娠14～20日）、20mg/kg以上で体重増加の促進（妊娠6～12日）、摂餌量の高値、40mg/kg以上で妊娠期間の延長がみられた。Seg IIのウサギ160mg/kgで1例が死亡し、1例が流産した。また、80mg/kg以上で糞便量の減少、体重増加の抑制及び摂餌量の低値がみられた。Seg IIIのラット3mg/kg以上でも摂餌量の高値がみられた。上記試験でみられた摂餌量の高値は本薬の薬理作用に起因した変化であると考えられた。

胚・胎児の観察では、Seg Iのラット20mg/kg以上で胎児体重の低値及び内臓変異発現率の高値がみられた。Seg IIのラット20mg/kg以上で胚・胎児死亡率の高値及び胎盤重量の高値、80mg/kgで胎児体重の低値がみられた。Seg IIのウサギ160mg/kgでも胚・胎児死亡率の高値がみられた。

出生児の観察では、Seg Iのラット10mg/kg以上に体重の低値及び形態分化・機能発達の遅延がみられた。Seg IIのラット40mg/kg以上で死産児数の高値、生存率の低値がみられ、80mg/kgでは出生時体重の低値もみられた。Seg IIIのラット10mg/kg以上に体重の低値及び形態分化・行動・機能発達の遅延がみられた。

（武田薬品・研究所）

2－4　その他の特殊毒性

（1）変異原性試験

細菌を用いた復帰突然変異試験なおいて変異原性はみられなかった。また、CHO細胞、AS52細胞及びマウスリンフォーマ細胞を用いた遺伝子突然変異試験においても突然変異誘発作用はなかった。CHL細胞を用いた染色体異常試験及びマウス小核試験では染色体及び小核の増加はみられず、さらに、ラットの肝細胞を用いたUDS試験ではDNA損傷作用はなかった。

（武田薬品・研究所）

（2）がん原性試験

動 物 種	投与経路・期間	投与量（mg/kg/日）	試 験 結 果
ラット	経口・24カ月	♂：0.9、3.6、7.3、14.5、57.1 ♀：0.9、3.6、14.5、57.1	低頻度の膀胱腫瘍 ♂：≧3.6mg/kg/日 ♀：陰性
マウス	経口・24カ月	2.7、9.1、27.2、90.7	陰性

投与量及び試験結果はピオグリタゾンとして表示

3.6mg/kg以上の雄ラットにおいて、低頻度の膀胱移行上皮の腫瘍がみられた。なお雌ラット及び雌雄マウスにおいては、いずれの組織・器官においても腫瘍原性はなかった。膀胱の増殖性病変を示したラットの約60％に結石等の石灰化に関連した病理組織所見が付随してみられ、膀胱腫瘍と尿結石あるいは尿中結晶等との関連性が示唆された。
そこで、さらにラット主要尿中代謝物の変異原性、結石の成分及び本薬を投与したラットの尿性状について検討するとともに文献的考察を加えた結果、本薬は代謝物を含めて変異原性はなく、本薬の投与によりラット尿性状に変化が生じ、ときに膀胱上皮に腫瘍を含む増殖性病変を誘発したものと考えられた。本薬による膀胱腫瘍はラットに特異的であると推察された。

（武田薬品・研究所）

（3）その他

本薬の代謝物M－Ⅱ、M－Ⅲ、M－Ⅳ及びM－Ⅴのマウス単回投与毒性試験では、それらの毒性は原薬と同等かあるいは弱かった。M－Ⅳのイヌ反復投与毒性試験の中及び高用量では、原薬と同様の毒性変化がみられた。また、類縁物質Ⅰをピオグリタゾン塩酸塩に混合して投与、あるいは暴露したラットの亜急性毒性試験及び変異原性試験において、新たな毒性の発現及び毒性の増強はなかった。

（武田薬品・研究所）

X：管理的事項に関する項目

1. 規制区分

注意—医師等の処方せんにより使用すること

2. 有効期間又は使用期限

3年

(外箱に表示の使用期限内であっても開封後はなるべく速やかに使用すること。)

3. 貯法・保存条件

全製剤共通

室温保存

OD錠の場合

開封後も湿気を避けて保存すること。(本品は高防湿性の内袋により品質保持をはかっている。)

4. 薬剤取扱い上の注意点

4－1 薬局での取り扱いについて

該当しない

4－2 薬剤交付時の注意（患者等に留意すべき必須事項等）

○循環血漿量の増加によると考えられる浮腫が短期間に発現し、また心不全が増悪あるいは発症することがあるので、患者には服用中の浮腫、急激な体重増加、症状の変化に注意し、異常がみられた場合には直ちに本剤の服用を中止し、受診するよう指導すること。

○本剤は他の糖尿病用薬と併用した場合に低血糖症状を起こすことがあるので、これらの薬剤との併用時には患者に対し低血糖症状及びその対処方法について十分説明し、注意喚起すること。

○PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。

5. 承認条件等

該当しない

6. 包　装

アクトス錠15	：PTP包装：	100錠（10錠×10）、420錠（14錠×30）、500錠（10錠×50）
	バラ包装：	500錠
アクトス錠30	：PTP包装：	100錠（10錠×10）、420錠（14錠×30）、500錠（10錠×50）
	バラ包装：	500錠
アクトスOD錠15	：PTP包装：	100錠（10錠×10）、420錠（14錠×30）、500錠（10錠×50）
アクトスOD錠30	：PTP包装：	100錠（10錠×10）、420錠（14錠×30）、500錠（10錠×50）

7. 容器の材質

アクトス錠

PTP：ポリプロピレン、アルミニウム箔

内袋：ポリエチレンとアルミニウムのラミネートフィルム

乾燥剤

ガラス容器、金属キャップ

紙箱

アクトスOD錠

PTP：ポリクロロトリフルオロエチレンとポリプロピレンのラミネートフィルム、
アルミニウム箔

内袋：ポリエチレンテレフタレートとポリエチレンのラミネートフィルム

乾燥剤

ポリエチレン瓶、ポリプロピレンキャップ

紙箱

8. 同一成分・同効薬

同一成分薬：なし

同　効　薬：糖尿病用薬

9. 国際誕生年月日

1999年7月31日

10. 製造販売承認年月日及び承認番号

アクトス錠

承認年月日：1999年9月22日

承 認 番 号：錠15：21100AMZ00642

錠30：21100AMZ00643

アクトスOD錠

承認年月日：2010年1月15日

承 認 番 号：OD錠15：22200AMX00046

OD錠30：22200AMX00047

11. 薬価基準収載年月日

アクトス錠

1999年11月19日

アクトスOD錠

2010年5月28日

12. 効能又は効果追加、用法及び用量変更追加等の年月日及びその内容

(1) 2002年6月17日に「食事療法、運動療法に加えてα-グルコシダーゼ阻害剤を使用して十分な効果が得られずインスリン抵抗性が推定される2型糖尿病」に対して効能・効果が追加された。

(2) 2008年12月22日に「食事療法、運動療法に加えてビグアナイド系薬剤を使用して十分な効果が得られずインスリン抵抗性が推定される2型糖尿病」に対して効能・効果が追加された。

(3) 2009年3月24日に「食事療法、運動療法に加えてインスリン製剤を使用して十分な効果が得られずインスリン抵抗性が推定される2型糖尿病」に対して効能・効果が追加された。

13. 再審査結果、再評価結果公表年月日及びその内容

「本剤の有効性・安全性等について特に問題はない」とされ、「承認、効能・効果、用法・用量には変更ない」とされた（再審査結果通知：2009年12月21日）

14. 再審査期間

6年（2005年9月21日満了）

15. 投薬期間制限医薬品に関する情報

該当しない

16. 各種コード

製剤	HOT番号	厚生労働省薬価基準収載医薬品コード	レセプト電算コード
アクトス錠15	108756701	3969007F1024	610432040
アクトス錠30	108757401	3969007F2020	610432041
アクトスOD錠15	119909301	3969007F3027	621990901
アクトスOD錠30	119910901	3969007F4023	621991001

17. 保険給付上の注意

該当しない

XI：文　献

1. 引用文献

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2. その他の参考文献

該当しない

XII：参考資料

1. 主な外国での発売状況

ピオグリタゾン塩酸塩は米国、カナダ、ドイツ、イギリス、フランスなどで発売されている。

2. 海外における臨床支援情報

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m2, respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m2). There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

本邦での使用上の注意「妊婦、産婦、授乳婦等への投与」は下記のとおりである。

(1) 妊婦又は妊娠している可能性のある婦人には投与しないこと。[妊娠中の投与に関する安全性は確立していない。また、ラット器官形成期投与試験では、40mg/kg以上の群で胚・胎児死亡率の高値、出生児の生存率の低値が、ウサギ器官形成期投与試験では、160mg/kg群で親動物の死亡又は流産がそれぞれ1例、胚・胎児死亡率の高値がみられている。]

(2) 授乳中の婦人に投与することは避け、やむを得ず投与する場合は授乳を中止させること。[ラットで乳汁中への以降が報告されている。]

XIII：備　　考

その他の関連資料

該当しない